THE STUDY OF IMPLEMENTATION OF RENAL STANDARDS

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Contents

Tables, Graphs and Figures

Abbreviations

A&E	*Accident and Emergency Department*
AOR	*Adjusted odds ratio*
APD	*Automated peritoneal dialysis*
ARF	*Acute renal failure*
AV	*Arterio-venous*
AVF	*Arterio-venous fistula*
BP	*Blood pressure*
BSA	*Body surface area*
Ca	*Calcium*
CABG	*Coronary artery bypass graft*
CAPD	*Continuous ambulatory peritoneal dialysis*
CCF	*Congestive cardiac failure*
CCPD	*Continuous cyclical peritoneal dialysis*
CI	*Confidence interval*
COPD	*Chronic obstructive pulmonary disease*
CKD	*Chronic kidney disease*
CRF	*Chronic renal failure*
EPO	*Erythropoietin*
ESRD	*End stage renal disease*
ESRF	*End stage renal failure*
Fe	*Iron*
g/dl	*Grams per decilitre*
g/l	*Grams per litre*
GFR	*Glomerular filtration rate*
GN	*Glomerulonephritis*
GP	*General practitioner*
Hb	*Haemoglobin*
HD	*Haemodialysis*
HIV	*Human immuno-deficiency virus*
HRQL	*Health related quality of life*
IPD	*Intermittent peritoneal dialysis*
kg	*Kilograms*
L	*Litres*
LVH	*Left ventricular hypertrophy*
MI	*Myocardial infarction*
µg/dl	*Micrograms per decilitre*
µg/l	*Micrograms per decilitre*
ml/min	*Millilitres per minute*
µmol/l	*Micro-moles per litre*

mmHg	*Millimetres of mercury*
mmol/l	*Milli-moles per litre*
MRI	*Manchester Royal Infirmary*
NHS	*National Health Service*
NICE	*National Institute for Clinical Excellence*
NIPD	*Nightly intermittent peritoneal dialysis*
NSF	*National Service Framework*
NYHA	*New York Heart Association*
OR	*Odds ratio*
PD	*Peritoneal dialysis*
pg/ml	*Pico grams per millilitre*
pmp	*Per million population*
PO	*Phosphate*
PTH	*Parathormone*
RCT	*Randomised control trial*
RF	*Renal failure*
RRF	*Residual renal function*
RRT	*Renal replacement therapy*
RVD	*Renovascular disease*
SD	*Standard deviation*
SIRS	*Study of implementation of renal standards*
SVS	*Society of Vascular Surgeons*
TIBC	*Total iron binding capacity*
TX	*Transplant*
UDRDS	*United States Renal Database System*
UF	*Ultra filtration*
UKM	*Urea kinetic modelling*
URR	*Urea reduction ratio*

ABSTRACT OF THESIS submitted by Anubha Trehan for the Degree of MD and entitled "The Study of Implementation of Renal Standards". *April 2008.*

AIM 1: To determine whether implementation of current national standards in relation to their achievement or non-achievement, improves outcomes in ESRD patients, receiving dialysis. Improving rates of achievement of the access standard, by creating more AV fistulas will improve mortality in ESRD patients. There is also sufficient data to justify the use of the Renal Association (RA) standard for phosphate control as a measure for good treatment on dialysis. This would suggest that other measures for dialysis "adequacy", of which the urea clearance is but one, are used when assessing good dialysis treatment. *AIM 2: To assess the impact on outcomes in ESRD patients, receiving dialysis, of non-treatment factors (for example, ethnicity and socio-economic factors) at the start of dialysis treatment.* Patients with higher levels of social deprivation (and patients from ethnic minorities have high levels of social deprivation) are at greater risk of having diabetes and being referred late to renal services. This suggests that targeting screening programs for the early detection of renal disease to socially deprived areas, including people with diabetes and from ethnic minorities, are likely to produce the biggest benefits in managing chronic kidney disease. *AIM 3: To assess the impact of mode of referral to nephrology services and dialysis modality, including haemodialysis access, on outcomes in patients with ESRD.* Improving referral of patients with chronic renal failure, followed by early dialysis planning, is likely to improve outcomes. Allowing more patients to start haemodialysis with a fistula may improve outcomes, especially admission with sepsis and mortality. *AIM 4: To report the strongest predictors of outcomes in terms of mortality, transplantation and hospitalisation in patients with ESRD, receiving dialysis.* Our study suggests; older age, multi-system disorders causing ESRD, co-morbidity, low serum albumin and high serum phosphate are reliable indicators of mortality after initiation of dialysis, and can be used to predict poor outcome. The ESRD population is getting older and has more co-morbidity, and it is possible that increasing transplantation in this group will lead to better outcomes, as well as be cost effective to the NHS. Further work needs to be done to suggest benefit versus harm of renal transplantation in this group. Improving haemodialysis access, improving early referral of patients with chronic kidney disease and using less peritoneal dialysis will reduce hospital admissions with sepsis. To reduce vascular episodes treatment for vascular risk factors needs to start much earlier than initiation of dialysis.

DECLARATION

No proportion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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DEDICATION

This thesis is dedicated to my parents, Dr Vijay Trehan and Mrs Santosh Trehan

SPECIAL MENTION

For my twin sisters, Nidhi and Vidhi Trehan

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My fellow researchers, especially Mrs Jean Winterbottom, and Mrs Beverley Lane, for their hard work, support and companionship.

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Chapter 1: Introduction

End stage renal disease (ESRD) that is untreated is fatal. The ideal outcome of ESRD treatment would fully restore all the functions of the kidney and give patients the same length and quality of life as people with normal kidneys. However, with current technology this is not possible. Therefore treatment of ESRD should aim towards the best use of resources and technology available to keep patients alive.

There are many different factors which impact on patient outcomes. These can be grouped into those related to the actual treatments, health service provision of treatment and patient characteristics.

Currently, health care providers worldwide are adopting an evidence based approach to their practice to improve patient outcomes. This is equally so for renal services, and has led to production of national guidelines and standards for the management of ESRD in many different countries. The strength of evidence supporting each guideline is variable and is sometimes based on expert opinion, in the absence of any appropriate research in particular areas. Clearly, it is possible for personal bias and financial constraints of health service provision to colour the recommendations. This is evident from differing guidelines produced by different countries for management of the same condition based on the same pool of evidence.

It is important to assess the impact on outcomes in patients receiving renal replacement therapy (RRT) for ESRD of implementing the national standards, as produced by the UK Renal Association. It is equally important to find the barriers to implementing these standards at a local level.

1.1. End stage renal disease (ESRD)

Kidneys are important in maintaining the body's homeostasis. They do this in several ways. Excretion of 'waste products' from various metabolic processes in the body, and maintaining strict fluid, electrolyte and acid-base balance are key functions. The kidneys also produce hormones, the most important of which are renin (important in the control of blood pressure), erythropoietin (important in the production of erythrocytes) and 1, 25-dihydroxyvitamin D_3 (important in maintaining normal bone).

Diseases affecting the kidney are traditionally divided by the site of the structural abnormality, i.e. glomerulus, interstitium, tubule and blood vessel, and by whether the disease affects organs other than the kidney. However, with time, an abnormality in any part of the kidney will affect the function of all the other structures and the kidney will be unable to maintain its homeostatic function. This is reflected by a reduced glomerular filtration rate (GFR - normal is an average of 120 ml/min) and an elevated concentration of blood urea and creatinine. The decrease in GFR and the elevation of 'waste products' results in specific signs and symptoms affecting other organ systems in the body. The resulting symptom complex is termed uraemia.

1.1.1. Definition of ESRD

A person is considered to have ESRD when their kidneys are irreversibly damaged and they have the signs or symptoms of uraemia *(Renal Association 1995)*. ESRD requires life-long RRT for continued survival and well being. As patients can present late in the course of their illnesses it is not always apparent at presentation whether they have ESRD or acute renal failure. Other patients thought initially to have ESRD may become dialysis independent, which suggests a reversible element to their renal disease. Therefore, for the purpose of epidemiological research the definition of ESRD needs to account for the diagnostic uncertainty which can occur at presentation.

In the United States Renal Database System (USRDS) for patients with ESRD, only patients who have received 90 days of continuous RRT are considered to have ESRD. This definition is accepted by most other ESRD registries worldwide. However in the UK, it was felt that this definition missed a significant proportion of patients with ESRD, who

have high mortality and morbidity rates within the first 90 days of their renal replacement therapy *(UK Renal Registry)*. Therefore the UK Renal Registry definition, which is accepted by the Renal Association, for a patient with new ESRD is: *"one who is accepted for treatment and transplanted or dialysed for more than 90 days or one who is diagnosed as having ESRD (i.e. accepted for dialysis in the anticipation they will need RRT indefinitely), dialysed, and dies within 90 days or one who is dialysed initially for acute renal failure but is subsequently diagnosed as having ESRD" (Renal Association 1997; Renal Association 2002).*

1.1.2. Diseases leading to ESRD

There are many (100+) diseases affecting the kidney which can lead to ESRD. The European Renal Registry has coded and grouped these conditions based on which part of the kidney the primary pathology occurs and whether other organ systems are involved *(Annual Report 1998. ERA-EDTA Renal Registry)*. The groups are shown in table 1.1.

Table 1.1. ERA-EDTA Primary Renal Groups

Group 1: Glomerulonephritis
Group 2: Interstitial Nephropathies
Group 3: Multi-system diseases
Group 4: Diabetic nephropathy
Group 5: Unknown/Other

Age also impacts on the distribution of causes underlying ESRD. The incidence of atherosclerotic renovascular disease becomes more prominent with increasing age. This and other age-related differences are depicted in table 1.2.

Table 1.2. Distribution, by age, of primary renal diagnosis in incident patients with ESRD from 2002 cohort *(UK Renal Registry. Sixth Annual Report. 2003).*

	Age <65 years	Age >65 years
Unknown	17.5 %	26.5 %
Diabetes	20.4 %	14.5 %
Glomerulonephritis	13.5 %	6.5 %
Pyelonephritis	6.7 %	6.3 %
Polycystic kidney	9.9 %	3.0 %
Hypertension	5.1 %	5.9 %
Renovascular disease	2.8 %	11.2 %
Other	14.4 %	12.6 %

Survival on RRT has been shown to be affected by the primary renal diagnosis causing ESRD. Data from the registry of the European Renal Association (table 1.3) shows this clearly. In addition, multi-system disorders such as diabetes and atherosclerotic renovascular disease are associated with significant other co-morbidity *(Chantrel et al. 1999).* Multivariate analysis reveals that the impact of primary renal diagnosis on mortality and morbidity is heavily influenced by age and co-morbidity *(Chandna et al. 1999; Metcalfe et al. 2000).* Conditions such as glomerulonephritis, polycystic kidneys and pyelonephritis which occur in younger people and are not associated with significant co-morbid illnesses, have the best survival outcomes. Diabetes, although occurring predominantly in the middle-age group, is associated with significant vascular co-morbidity and therefore has poor survival. Renovascular disease/hypertension, occurring mainly in the elderly also has poor survival because of age related and other co-morbidity. Certain primary renal diagnoses, e.g. myeloma have a huge impact on morbidity and mortality, which is almost independent of age and co-morbidity *(Chandna et al 1999.).*

Table 1.3. 90 day, one- and two-year survival probabilities (1996-2000 cohort) of incident RRT patients, by primary renal diagnosis, adjusted for age and gender *(EDTA-ERA Renal Registry 2002 Annual Report).*

	90 day survival (%)	1 year survival (%)	2 year survival (%)
Diabetic nephropathy	**93.5**	**78.8**	**61.1**
Hypertension/Renovascular disease	**91.5**	**76.8**	**62.3**
Glomerulonephritis	**96.3**	**90.1**	**81.8**
Other renal disease	**92.5**	**80.4**	**68.8**

1.1.2.1. Diabetic Nephropathy

Diabetic nephropathy has become the single most common diagnosis of patients with ESRD who start RRT in the developed world *(USRDS Annual Data Report 2004; EDTA-ERA Renal Registry 2002 Annual Report; UK Renal Registry Tenth Annual Report 2007).*

The take on rate of new ESRD patients secondary to diabetes mellitus (mainly type 2) has increased progressively in the past decades, first in the United States and Japan, but subsequently in all countries with a western lifestyle *(Ritz et al 1999.).* This is a consequence of the increasing incidence of type 2 diabetes in the general population. The more widespread availability of dialysis only partly explains this phenomenon *(Hasslacher et al.1989; Nelson et al.1993).*

Diabetic patients starting RRT bring with them a heavy burden of co-morbid illnesses. One series in France found that of 84 consecutive patients with type 2 diabetes starting dialysis, 67% had had at least one episode of left ventricular dysfunction, 64% were hypertensive (despite treatment), 36% had angina, 26% a previous myocardial infarct, 37% were unable to walk independently and 16% had had at least one limb amputated *(Chantrel et al.1999).* Diabetic patients also have more difficulties with dialysis treatment with increased risks of arterio-venous (AV) fistulae failure *(Konner 2000; Lin et al.1998)*, peritonitis and exit site infections on peritoneal dialysis *(Huang et al. 2001; Marcelli et al. 1996)*, an increased rate of decline of residual renal function (RRF) on peritoneal dialysis *(Canada-USA (CANUSA)*

Peritoneal Dialysis Study Group 1996), and malnutrition *(Avram et al. 2001)*. All these factors need to be taken into account, as well as factors which impact on outcome in non-diabetic patients, to improve the outcomes of dialysis in diabetic patients.

Overall diabetic patients treated for ESRD have a 20-25% lower survival than age-adjusted non-diabetic patients *(USRDS Annual Data Report 2004; Charra et al. 1994[a]; Marcelli et al. 1996; UK Renal Registry. Tenth Annual Report 2007)*. Diabetic nephropathy is also associated with increased hospitalization *(Becker et al.1999)*.

1.2. Dialysis and Outcomes

Treatment for ESRD is termed renal replacement therapy (RRT) and consists of haemodialysis (HD), peritoneal dialysis (PD) or transplantation (TX) and must be continued for the remaining years of a patient's life. It is possible to manage patients who do not wish to undergo RRT by conservative means (non-dialysis related); a study from UK showed that survival in the high risk group was the same whether patients received dialysis therapy or not (Smith et al. 2003). Dialysis (HD and PD) is the main treatment modality for the majority of patients with new ESRD and for prevalent patients (see table 1.4).

Table 1.4. Percentage of incident and prevalent patients on different renal replacement modalities *(UK Renal Registry. Sixth Annual Report 2003; UK Renal Registry. Tenth Annual Report. 2007).*

	Incident patients (day 90) (%)			Prevalent patients (%)		
	TX	HD	PD	TX	HD	PD
2002	2.7	68.8	28.5	46	38.7	14.8
2006	5	73	22	45	44	11

It is possible to look at outcomes on dialysis of patients undergoing RRT in various ways and there are both objective and subjective means of assessing these. The commonly accepted outcomes are:

1. Survival on dialysis or RRT

2. Morbidity and hospitalisation

3. Quality of life and functional status on dialysis

4. Change of therapy on dialysis especially the need to change from one dialytic mode to another.

All these are influenced by the underlying disease and associated co-morbidities, age, the clinical state at presentation, the impact of dialysis related complications and the dialysis therapy itself and the quality of life at the onset of dialysis. These factors are inter-related and at times it is difficult to tease out what the crucial factors are. The following sections address some of these factors and complex inter-relationships and looks at those factors that form the basis of dialytic therapy and whether improvements in these parameters affect outcomes.

1.2.1. Haemodialysis

The first experimental haemodialysis was performed in dogs by Abel et al in 1913 at the Johns Hopkins Medical School in Baltimore *(Abel, Rowntree, and Turner 1913)*. Willem Kolff at the Groningen University Hospital in The Netherlands introduced the first dialyser suitable for use in man in 1943. However, problems of vascular access limited the use of dialysis to patients with acute renal failure who only needed dialysis for a short time *(Kolff et al. 1997)*. In 1960, the arterio-venous cannula system was introduced as vascular access for haemodialysis by Belding H. Scribner in Seattle in the United States *(Scribner et al. 1960)*, and 6 years later the surgically created arterio-venous fistula was introduced by Brescia et al *(Brescia et al. 1966)*. AV fistula remain the predominant choice of access for long-term dialysis, despite the introduction of woven polytetrafluoroethylene (PTFE) as material for implanted subcutaneous arterio-venous grafts by George Thomas in Seattle *(Thomas 1969)*. Indwelling semi-permanent catheters were introduced in 1969 by Josef Erben in Czechoslovakia and studied by Robert Udall et al in Canada *(Erben et al. 1969; Uldall et al. 1979)*. These were refined to produce double lumen catheters, initially the Vas-Cath and in 1988 the softer, silicone PermCath *(Twardowski 1988)*. For patients in whom a fistula cannot be fashioned, e.g. the elderly or diabetic patients, these catheters provide long-term dialysis access.

These new techniques for creating permanent vascular access made it possible to perform an unlimited number of dialyses in patients with chronic, irreversible renal failure. Self dialysis, by patients with ESRD in their own homes, was first suggested by Nose in 1961. It was started in the UK in 1964 by Shaldon *(Baillod and Moorhead 1975; Shaldon and McKay 1968).* It became very popular in the UK, but because of the level of training required for patients to use their dialysis machines it was suitable for young, fit people only. It was not suitable for elderly or infirm patients, who were, therefore, denied life-saving treatment.

1.2.1.1 Factors influencing outcomes of patients using haemodialysis

1.2.1.1.1. Haemodialysis Access

Background

An ideal access delivers a flow rate adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (e.g., infection, stenosis, thrombosis, aneurysm, and limb ischaemia). Although no current vascular access fulfills all of these criteria, the native arterio-venous (AV) fistula comes the closest to doing so. Studies demonstrate that native accesses have at best 4 to 5 year patency rates and require the fewest interventions compared to other access types *(Churchill et al. 1992).* Approximately 20% of patients will remain dependant on silastic cuffed catheters because of poor venous anatomy, and a much smaller number because of severe cardiac dysfunction *(Renal Association 2002)* (a high flow fistula can contribute to high output heart failure). There is wide geographic variation in the numbers of patients starting dialysis with AV fistula. In the UK 47% of patients who start haemodialysis start with AV fistula, 66% in Europe and 17% in the USA *(Hood et al. 1995; Pisoni et al. 2002).* In the UK, 2 main reasons have been suggested for the comparatively low rate of fistula formation. A large proportion of patients with ESRD will be hospitalised at initiation of dialysis and will use catheters for access, in the UK this accounts for up to 45% of patients *(Chesser and Baker 1999).* Early referral of chronic kidney failure patients to a nephrologist allows for access planning and thus increases the probability of AV fistula formation. The second reason is lack of surgical support in many renal units *(Renal Association 2002).*

As a result of current practice patterns, haemodialysis access failure is a major cause of morbidity for these patients. Catheters and grafts have higher rates of hospitalisation and sepsis compared with AV fistula *(Nassar and Ayus 2001;Schwab et al. 1999)*. The USRDS reports that haemodialysis access failure is the most frequent cause of hospitalisation among ESRD patients, and in some centres it accounts for the largest number of hospital days *(Mayers et al. 1992)*. A retrospective study in the USA, found that dialysing via a catheter was associated with a higher mortality, all cause and infection-related, than using an AV fistula *(Pastan, Soucie, and McClellan 2002)*.

In Europe, the Dialysis Outcomes and Practice Pattern Study (DOPPS), reporting on outcomes in randomly selected samples of haemodialysis patients from different countries has found a wide variation in access creation and use *(Rayner et al. 2003)*. Hospitalisation rates for vascular access-related infection ranged from 0.01 hospitalisations per patient year in Italy to 0.08 hospitalisations per patient year in the UK, consistent with the higher dialysis catheter use in the UK (25%) compared with Italy (5%) *(Rayner et al. 2004)*. These results suggest that a facility's preferences and approaches to vascular access practice are major determinants of vascular access use, even after adjustment for patient characteristics. A further study in the US suggested both dialysis catheters and grafts had a higher risk of mortality than use of AV fistula *(Dhingra et al. 2001)*. The CHOICE study of the effect of the type of vascular access on outcomes among 616 incident haemodialysis patients showed that the adjusted mortality ratio, compared with an AV fistula, was 1.2 for an arteriovenous graft and 1.5 for a central venous catheter *(Astor et al. 2005)*.

Defining and implementing optimum management for haemodialysis access is likely to improve patient outcomes. In the USA there were detailed NKF-K/DOQI clinical practice guidelines for vascular access from 2000 *(III. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access: update 2000)*. An active program of AV fistula creation in the US increased the prevalence of AV fistulae in HD patients from 24% to 44%, and this was associated with a significant reduction in hospitalisation rates *(Ackhad et al. 2005)*. In the UK, the Renal Association has recognised the importance of dialysis access. There was no standard for haemodialysis access in the second edition of the Renal Association guidelines; by 2002, the third edition, the recommendation was that 67% of patients who present within 3 months of needing dialysis should start with an AV fistula and in 80% of prevalent patients

and in the 4th edition of the Renal Association guidelines published in 2007, AV fistulae were recommended as access for as many patients as possible on haemodialysis *(Renal Association, 1997, 2002 & 2007-2008)*

1.2.1.1.2. Delivered haemodialysis dose

Background

The first measure of delivered dose of dialysis was based on the "square-meter/hour" hypothesis suggested by Babb and Scribner *(Babb et al. 1971)*. Using this, Babb developed a "dialysis index" in 1975 which was derived from measurements of body surface area, residual renal function, vitamin B_{12} clearance (not urea), dialysis membrane and ultrafiltration *(Babb et al. 1975)*. This did not gain any popularity at the time, based as it was on middle molecule clearance. The emphasis shifted to small molecular weight substances to assess delivered dose. The cardinal study was the National Cooperative Dialysis Study (NCDS), in 1978. This was a prospective, randomised, control trial designed to provide data concerning the relationship between the fractional clearance of urea and patient outcome *(Lowrie et al. 1981)*. In 1985, Sargent and Gotch suggested an urea based index, Kt/V *(Gotch and Sargent 1985)*. Urea is a small, readily dialyzed solute that is the bulk catabolite of dietary protein, constitutes 90% of waste nitrogen accumulated in body water between haemodialysis treatments and is easily measured in blood. To use this formula the reduction of plasma urea during dialysis, the length of dialysis and an estimation of the volume of distribution of body urea are needed. Of these measures only the duration of dialysis can be measured precisely and debate still continues as to how to best measure the other parameters. Lowrie and Lew proposed using only one parameter of the Kt/V equation, the reduction in urea, to make a simpler equation *(Chertow et al. 1999; Lowrie et al. 1999)*. This is known as the urea reduction ratio (URR) and equals the pre-dialysis urea minus the post dialysis urea divided by the pre-dialysis urea, expressed as a percentage.

To normalise for differences in the size of patients, a dose of haemodialysis is described as the fractional clearance of urea as a function of its distribution volume (Kt/V). The fractional clearance is operationally defined as the product of dialyser clearance (expressed as K and measured in liters per minute [L/min]) and the treatment time (expressed as t and measured in minutes); the volume of distribution of urea is expressed as V and measured in litres. Kt/V may be determined by formal urea kinetic modeling (UKM) or by

extrapolation from the fractional change in blood urea concentration during a dialysis session. The delivered dose of haemodialysis may also be assessed using the URR.

Several leading expert bodies have concluded that formal urea kinetic modeling (UKM), based on either two or three blood urea samples, was the best method for routine measurement of the dose of haemodialysis *(I. NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy: update 2000)*. However, it is the least simple to implement. The complexity of the calculations requires the use of computational devices and software. Physical parameters, such as the K and V, are difficult to measure and to monitor, and the actual treatment time can be difficult to determine. In addition, the time required for the dialysis unit staff to accurately collect and adequately process all patient information to support these calculations can be significant in large dialysis units. Finally, although the cost of the computers and software is low, it is a factor for some dialysis centres.

URR is the easiest method to quantify dialysis dose, in terms of calculation and collection, and has therefore become very popular in renal units. The URR has been shown to be a statistically significant predictor of mortality for ESRD patients *(Held et al. 1996; Owen, Jr. et al. 1993)*. The most serious disadvantage is that the URR does not account for the contribution of ultrafiltration to the final delivered dose of dialysis, in contrast to formal UKM and the Kt/V formulae *(Garred et al. 1994; Sherman et al. 1995)*. This is because the convective transfer of urea that occurs by ultrafiltration does not result in a decrease in the urea concentration, although urea removal into the dialysate has occurred. The result is that the URR is less accurate in estimating the delivered dose of haemodialysis than the single-pool, variable volume Kt/V calculated by formal UKM.

The double-pool method tries to account for serum urea rebound seen post dialysis. The extent of urea rebound varies greatly among adult patients. In one study, the mean amount of urea rebound, measured as the percent increase in post dialysis urea concentration immediately after dialysis versus 30 minutes after dialysis was 17% *(Leblanc et al. 1996)*. However, in some patients, the literature describes the occurrence of as much as 45% rebound or 19% to 75% error between single-pool and double-pool KT/V*(Abramson et al. 1994; Smye et al. 1994)*. On average, the equilibrated Kt/V (Kt/V_{equil}) is 0.2 units less than the single-pool Kt/V, but can be as great as 0.6 units less *(Daugirdas et al. 1997; Spiegel et al. 1995)*. For most patients, urea rebound is nearly complete 15 minutes after haemodialysis,

but for a minority of patients, it may require up to 50 to 60 minutes *(Pedrini, Zereik, and Rasmy. 1988).*

Impact of dialysis dose on outcomes

Numerous peer-reviewed studies have confirmed the association between the adequacy of the delivered dose of haemodialysis and patient outcome *(Collins et al. 1994; Fernandez et al. 1992; Gotch et al.1997; Hakim et al.1994; Held et al.1996; Lowrie et al. 1992; Lowrie 1994; Owen, Jr. et al. 1993; Owen, Jr. et al. 1998; Parker, III et al. 1994).*

Reanalysis of the primary data from the NCDS showed that Kt/V <0.8 was associated with a relatively high rate of patient morbidity, whereas Kt/V values between 1.0 and 1.2 were associated with a low rate of morbidity *(Gotch and Sargent 1985).* An observational study from the USA, also found that a dialysis dose of less than 1.2 was independently associated with longer and more frequent hospitalization *(Sehgal, Dor, and Tsai 2001).*

Uncontrolled retrospective studies suggested an improved survival with greater delivered doses of haemodialysis (Kt/V >1.2 and URR of 65%) *(Charra et al. 1992; Owen, Jr. et al. 1993).*

The HEMO study was a randomised clinical trial in 1846 patients undergoing thrice-weekly dialysis. It used a two-by-two factorial design to assign patients randomly to a standard or high dose of dialysis and to a low-flux or high-flux dialyser. In the standard-dose group, the mean (+/-SD) urea-reduction ratio was 66.3 +/-2.5 percent, the single-pool Kt/V was 1.32 +/-0.09, and the equilibrated Kt/V was 1.16 +/-0.08; in the high-dose group, the values were 75.2 +/-2.5 percent, 1.71 +/-0.11, and 1.53 +/-0.09, respectively. The primary outcome, death from any cause, was not significantly influenced by the dose or flux assignment. The main secondary outcomes (first hospitalisation for cardiac causes or death from any cause, first hospitalisation for infection or death from any cause, first 15% decrease in the serum albumin level or death from any cause, and all hospitalisations not related to vascular access) also did not differ significantly between either the dose groups or the flux groups *(Eknoyan et al. 2002; Owen, Jr. et al. 1998).*

These studies have lead to the Renal Association recommending a minimum Kt/V of 1.2 or URR >65% for patients receiving HD *(Renal Association 2002).*

1.2.1.1.3. Length of haemodialysis

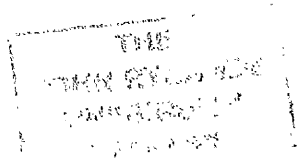
The delivery of dialysis was initially empirical without any measure of the dose of dialysis delivered. When it was found that 24 hour dialysis once a week failed to make patients better, it was changed to 12 hours twice a week and then 8 hours three times a week.

However the introduction of new dialysers with larger surface areas, led to shorter dialysis sessions through the 1970's *(Cambi et al. 1975)*. In the USA, where reimbursement costs for each dialysis had decreased and caused increased financial pressure on renal units, the time of dialysis sessions decreased even further than the average in Europe (4 hours) to 2.5 –3 hours in the 1980's, based on the NDCS conclusions which suggested that small molecule clearance was an adequate measure of dialysis adequacy. Furthermore, the practicality of 3 dialysis sessions during the day tended to fix a maximum dialysis session to 4 hours. Patient preference was also for shorter times spent on dialysis. These, and economic, arguments prevailed in spite of several studies which showed that short dialysis sessions, especially less than 4 hours three times a week, resulted in increased mortality *(Broyer et al.1983; Held et al. 1991; Lowrie and Lew 1990; Owen, Jr. et al 1998)*. Although dialysis sessions less than 3 times a week are strongly discouraged by experts in dialysis therapy *(Renal Association 2002)*, financial reasons and lack of haemodialysis facilities has led to many units providing less dialysis to their patients.

The most compelling evidence for long dialysis (>8 hours 3x per week) has come from Tassin, France. They reported 20-year actuarial survival experience for 445 unselected haemodialysis patients. They used the same dose of dialysis for all patients since beginning: 24 square meter hours of Kiil dialysis (cuprophane) per week with acetate buffered dialysate. Kt/V mean (SD) was 1.67 (0.41). Six months after starting dialysis, 98% of patients were normotensive and off all blood pressure medication. Survival rate was 87% at 5 years, 75% at 10 years, 55% at 15 years, and 43% at 20 years of HD *(Charra et al. 1994)*. It must be noted that patients accepted at this time were much younger, few had diabetes and had much less co-morbidity than patients accepted for dialysis today.

1.2.1.1.4. Daily haemodialysis

Since the introduction of haemodialysis, it was strongly felt that daily dialysis would produce better outcomes than intermittent dialysis, on the basis that the kidneys function continuously *(Kjellstrand and Ing 1998)*. Studies by Borah et al and Gotch et al have



confirmed that Kt/V varies considerably between dialysis and non-dialysis days, and that averaged Kt/V do not reflect the true clearances achieved by intermittent dialysis *(Borah et al. 1978; Gotch, Gentile, and Schoenfeld 1993)*. Dialysis access, inconvenience to patients and resources have remained the major blocks to widespread acceptance of this concept.

Several series have shown improved outcomes for patients with ESRD managed on daily regimes. Two main regimens are being investigated. One involves 2 hours dialysis daily for 6 days and the other slow dialysis overnight for 5-7 nights. Both regimens have been shown to produce better outcomes than conventional 4 hours dialysis 3 times a week *(Buoncristiani et al. 1988; Lindsay et al. 2003; Manohar et al. 1981)*.

1.2.2. Peritoneal dialysis

As an initial concept experiments with peritoneal dialysis, using animals and then human subjects, were started by Ganter et al in 1923. In 1959 a simplified method of intermittent irrigation of the peritoneal cavity, using a single, disposable catheter and commercially available dialysis solutions, was introduced *(Maxwell et al. 1959)*. With the introduction of a permanent, indwelling, silicone-rubber catheter with two Dacron cuffs, in 1968 *(Tenckhoff and Schechter 1968)*, peritoneal dialysis became similar in efficacy to haemodialysis *(Tenckhoff et al. 1973)*. However it was not until Popovich et al in 1976 *(Popovich 1976)* introduced the concept of a "portable/wearable equibrilation" technique, which was later to develop into the currently accepted continuous ambulatory peritoneal dialysis (CAPD), that peritoneal dialysis gained universal acceptance as a valid treatment for ESRD. CAPD became particularly popular in countries with government funded healthcare, e.g. UK, but was less popular in countries with privately funded dialysis services, e.g. US *(Nissenson et al. 1993)*.

Peritoneal dialysis also became popular in the elderly and diabetic patients. This was partly because this group of patients better tolerated the gentler demands of peritoneal dialysis on their cardiovascular system, but mostly because of financial considerations. As discussed earlier these groups of patients have a much higher mortality on dialysis and the comparatively poor outcomes led to the opinion amongst critics that peritoneal dialysis was a *"second class treatment for second class patients" (Shaldon et al. 1985)*. However, later studies have suggested that in similar patients outcomes are comparable *(Burton and Walls 1987; Gokal and Mallick 1999; Gokal et al. 1987)*. The biggest problem with CAPD is technique survival (discussed later) that limits its use to less than 10 years, with only a few exceptions *(Oreopoulos et al. 1981)*.

The physiological basis of dialysis across the peritoneum entails the processes of diffusion, convective transport, and osmosis. The concept of CAPD modeled by Popovich et al in 1976 utilizes the smallest volume of dialysate, that is, the least dialysate flow rate to prevent uraemia. Using a double-pool model, they demonstrated that the accumulation of a metabolite in the body would be equal to the generation rate minus the combined effect of the residual renal function and overall dialysate clearance. Using this, they put forward the theory that a patient will maintain a steady blood urea of about 30 mmol/l if 10 litres of peritoneal dialysis fluid are allowed to equilibrate with body fluids and, with ultrafiltration, a total dialysate of 12 litres daily. This was later modified for practical reasons to 4 daily exchanges of 2 litres, which became the standard CAPD regimen.

If 2 litres of fluid are allowed to dwell in the peritoneal cavity until equilibration has been achieved, then the drained volume will equal the urea clearance. Popovich et al showed that the number of exchanges would affect the clearance of urea (or as is more commonly used to measure the solute clearance in peritoneal dialysis, fractional urea clearance or Kt/V). Further theoretical analysis by Teehan et al *(Teehan, Schleifer, and Brown 1990)* has shown that the maintenance of a steady level of urea on CAPD is dependent on the daily volume of fluid exchanged, the size of the patient, and the residual renal function.

The removal of excess fluid is a critical factor in any form of dialysis; in peritoneal dialysis this has traditionally been achieved by adding to the solutions various concentrations of glucose, which act as the osmotic driving force. The transperitoneal ultrafiltration rate is governed primarily by a complex interplay between the peritoneal membrane and physiological forces across it – osmotic and oncotic forces. Osmotic fluid flow between two isosmotic solutions can occur if they are separated by a permeable membrane and contain solute components with differing reflection coefficients *(Mistry, Mallick, and Gokal 1987)*. This is the basis of colloid osmosis, similar to that induced by albumin across the capillary wall. During peritoneal dialysis, water may be transferred across the peritoneal capillary in either direction depending on hydrostatic, oncotic, and crystalloid osmotic pressure. The intra-peritoneal re-absorption of dialysate during peritoneal dialysis involves at least two pathways— lymphatic and transcapillary (venular) fluid absorption in response to Starling forces.

Automated peritoneal dialysis

Automated peritoneal dialysis (APD) is a broad term that is used to refer to all forms of peritoneal dialysis employing a mechanical device to assist in the delivery and drainage of the dialysate from the peritoneal cavity.

Continuous cyclical peritoneal dialysis (CCPD) is based on the same principle as continuous ambulatory peritoneal dialysis but uses a cycler (automated machine) to allow exchange of peritoneal fluids overnight. It was developed as an alternative to CAPD for patients who were incapable of performing manual exchanges or unwilling to interrupt their daily routine for dialysis exchanges *(Diaz-Buxo et al. 1981)*. Technically, CCPD is a reversal of CAPD, where the shorter exchanges are automatically provided at night while the longer exchange is made during the day. It is possible to have the peritoneum empty during the day (dry day – regime called nightly intermittent peritoneal dialysis (NIPD)) but in order to compensate for inadequate solute removal patients usually need one or two exchanges done in the daytime ('wet' day). Now, with the availability of icodextrin, the entire diurnal exchange can be undertaken by a single exchange of this solution, because it is able to achieve sustained ultrafiltration with prolonged (8-16 hours) dwell times *(Mistry, Mallick, and Gokal 1987)*. Patients with a hyperpermeable membrane are particularly suitable to APD (short night dwells achieves better ultrafiltration) - it is in this very situation that icodextrin can be used during the long daytime dwell to enhance UF and, secondarily, solute clearance *(Krediet and Mujais 2002)*.

During *tidal peritoneal dialysis* a portion of the dialysate is drained and then replaced by fresh peritoneal dialysis fluid with each cycle. The majority of the dialysate is in constant contact with the peritoneal membrane until the end of the dialysis and this method improves solute and water clearance.

1.2.2.1. Factors influencing outcomes of patients using peritoneal dialysis

1.2.2.1.1. Quantification of delivered dialysis dose

Background

The principles of peritoneal dialysis as proposed by Popovich and Teehan form the basis of quantification of dialysis dose *(Popovich et al. 1976)*. The use of Kt/V for solute clearance was first applied to PD using the HD experience in the National Cooperative Dialysis Study *(Lysaght et al. 1989)*. The difference in HD and PD Kt/V values, with HD Kt/V being higher than PD Kt/V result from HD being an intermittent therapy, whereas PD is a continuous one *(Keshaviah, Nolph, and Van Stone 1989)*.

The fractional clearance of urea, expressed as Kt/V, which is urea clearance (K) per unit time (t) related to total body water (V). Kt is obtained by multiplying the effluent: blood urea nitrogen concentration ratio (D/Purea) by the 24 hour effluent drain volume. Renal urea nitrogen clearance is added to this. The daily value is multiplied by 7 to provide a weekly value, which is then normalized to a function of patient size: for urea, the volume of urea distribution (v) calculated from the Watson normogram is used, or can be estimated as 60% of body weight in males and 55% of weight in females. Creatinine clearance (both peritoneal and residual renal) is also obtained from a 24 hour collection of dialysate, to which is added the average of the renal creatinine and urea nitrogen clearance (since creatinine clearance overestimates glomerular filtration rate due to tubular secretion of creatinine). An adjustment for body surface area is also required. Creatinine clearance is normalized to body surface area (BSA) or (K × 1.73/BSA)

Major changes in clinical status (e.g., patient compliance, weight gain, weight loss, technical/mechanical complications, some causes of hospitalisation) may alter PD dose requirements and therefore require re-evaluation of the Kt/V. Loss of residual kidney function is the major cause of decreasing clearance in PD subjects followed longitudinally. The CANUSA study demonstrated substantial loss of kidney function at 6-month intervals and was the only predictor of outcomes *(CANUSA 1996)*.

Retrospective studies have suggested that a weekly Kt/V less than 1.65 is associated with poor outcomes *(Genestier et al. 1995)*. Clinical studies addressing the validity of these predictions can be divided into those using univariate and those using multivariate statistical analyses. Three studies from France, Italy, and North America have used multivariate statistical analysis *(CANUSA 1996; Genestier et al. 1995; Maiorca et al. 1995)*. The French study found better survival among patients with an initial weekly Kt/V >1.7 but did not evaluate changes in Kt/V associated with loss of residual kidney function. The Italian study evaluated prevalent CAPD patients with minimal residual kidney function. Improved patient survival was observed with a weekly Kt/V>1.96. Values higher than 1.96 were not associated with increased survival but the statistical power to detect this association was low. The CANUSA study of 680 incident continuous peritoneal dialysis patients reported a 5% decrease in patient survival in association with every 0.1 decrease in total weekly Kt/V, for Kt/V between 1.5 and 2.3. The predicted 2-year survival associated with a constant total Kt/V of 2.1 was 78%. These predictions assume that renal and peritoneal Kt/V are equivalent.

This led to some authorities recommending a minimum weekly Kt/V greater than 2.0 and a weekly creatinine clearance greater than 60 l/1.73 m^2 *(II. NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy: update 2000)*. In UK, there was a more conservative approach to the minimal clearance target (Kt/V >1.7 and weekly creatinine clearance >50L *(Renal Association 1997)*).There was a need for a good randomised controlled study (RCT). Two such studies have provided evidence from which to arrive at minimal clearance targets. One was the ADEMEX study *(Paniagua et al. 2002)*, a prospective randomised control trial with 968 new and prevalent CAPD patients followed up for a minimum of 2 years. Patients were randomised to control (standard 4x2L regime to achieve a peritoneal clearance of Kt/V 1.6-1.8 and creatinine clearance 45-50L/week) or treated groups (4x 2.3-3.0L regime to achieve targets of Kt/V 2.0 and creatinine clearance 55-60L/week). There was no difference in survival between the 2 groups and no impact on survival in relation to albumin (< or > 30g/l), diabetes, protein intake (normalised protein nitrogen appearance < or > 0.8g/kg/day), anuria, transport profile and body size. In addition there was no difference in hospitalisation or peritonitis rates between the treatment and control groups. The other randomised, prospective study in 331 new CAPD patients, was conducted in Hong Kong *(Lo et al. 2003)*. Patients were randomised into 3 groups of Kt/V: 1.5-1.7, 1.7-

2.0, >2.0 and followed for 2 years. There was no difference in survival between the 3 groups. However there were more patients in 1.5-1.7 group with clinical problems requiring withdrawal from study (higher demand for erythropoietin and slightly higher hospitalisation rate), but no difference in nutritional status. There was no significant difference between the latter 2 groups. These studies support the Renal Association guideline recommending a minimum Kt/V of 1.7 *(Renal Association 2002).*

The above studies were all done in patients receiving CAPD, there are no such studies to suggest the levels of Kt/V needed to improve outcomes in APD nor studies that delineate a optimum target beyond which there are no further improvements in outcomes. Theoretically, there is an 8% difference in clearance between CAPD and NIPD. Nowadays there is very little NIPD practiced and all of peritoneal dialysis represent continuous therapies – hence the same targets are probably applicable to both CAPD and APD.

1.2.2.1.2. Technique failure

One of the biggest causes of morbidity in a patient using peritoneal dialysis is technical failure resulting in the need to transfer PD patients to HD. This was excessive in the eighties and was much greater than the need to transfer patients from haemodialysis to PD *(Gokal et al. 1999).* However, in the nineties, several studies showed an improvement in these complication rates *(Lupo et al. 1992; Maiorca et al. 1999; Marichal et al. 1990).* Peritoneal dialysis success rates have continued to improve over the last decade. Data from UK Renal Registry, studying a 3 year cohort from 1999-2001, found a 1 year PD technique failure rate of 11.7%, but transfer from PD to HD is still more common the reverse *(UK Renal Registry. The Sixth Annual Report 2003).* This improvement has also been shown in the US in >40,000 patients using CAPD and APD between 2000-2003 *(Mujais S and Story K. 2006).*

Table 1.5. Causes of technique failure in long-term peritoneal dialysis patient from 6 cohort studies in the nineties *(modified from Davies et al 1998).*

	Recurrent peritonitis	Ultrafiltration failure	Leak	Other	Patient choice
Maiorca *(1991)*	48.8%	22.1%	10.9%	11.9%	13%
Lupo *(1991)*	29%	16.4%	8.5%	13.3%	11%
Maiorca *(1996)*	37%	9%	4%	13%	37%
Kawaguchi *(1997)*	13.6%	23.5%	2.3%	44%	15.2%
Davies *(1998)*	54%	27%	2%	-	17%
Van Biesen *(2000)*	50%	25%	11%	-	14%

Overall peritonitis rates can be influenced by the centre (see table), the particularly low rates of peritonitis seen in Japan are partly due to prolonged and better training, improved connection devices and less co-morbidity. An association between malnutrition and frequency of peritonitis has been reported *(Genestier et al. 1995; Young et al. 1986)*. A Cochrane systematic review has also concluded that Y-set/disconnect and flush peritoneal dialysis systems significantly reduce the risk of peritonitis *(Genestier et al. 1995; Strippoli et al. 2004)*. These advances have led to lower peritonitis rates and improved technique survival, but it still remains a significant problem *(Davies et al. 1998; Genestier et al. 1995)*. The major problem is gram negative and fungal infections, which have not shown a decline with introduction of disconnect systems.

Inadequate dialysis is directly responsible for at least 20% of transfer to HD in long-term patients. There is an association between PD technique failure and total solute clearance *(Tattersall et al. 1994)*, and one possible reason for poor technique survival rates may be underlying inadequate dialysis. While the CANUSA study found a relationship between creatinine clearance and PD technique survival, the investigators suspected this was more related to RRF than delivered dose of PD and Bargman et al reanalysed the CANUSA study data and found the most important factor was urine volume *(Bargman, Thorpe, and Churchill 2001)*. It is now clear from various studies that fluid removal is especially difficult *(Ates et al. 2001)*. The EAPOS study of APD in anuric patients showed excellent 2 year survival; the differentiating factor was volume of ultrafiltration at start of the study;

>750ml/day had a significantly better survival than the group with ultrafiltration <750ml *(Brown et al. 2003).*

1.2.3. Haemodialysis versus Peritoneal Dialysis

Choice of therapy is controversial and is dictated predominantly by non-medical factors. In a study by Nissenson et al., five non-medical factors were enunciated—the most important reason for selecting a particular mode of dialysis turned out to be financial and reimbursement policies *(Nissenson et al. 1993).* When differences in reimbursement for physicians or facilities were substantial, the utilisation rates varied concomitantly. In countries with fixed annual allocations, the utilisation of peritoneal dialysis was high, reflecting lower costs and diminished maintenance of HD facilities. In countries where financial aspects were less prominent, other factors such as physician bias and social mores took on greater importance. There is greater penetration of peritoneal dialysis in countries with a greater share of public providers of dialysis; in mixed economies the PD penetration is less and minimal in a system of private providers *(Horl, De, and Williams 1999).*

Another important factor that impacts on modality selection is patient education prior to the need for dialysis. Several studies show that, where this is deficient than there is bias towards HD. In the US, the USRDS in 1997 reviewed the patient reported process of modality choice *(The USRDS Dialysis Morbidity and Mortality Study: Wave 2. United States Renal Data System 1997).* In this analysis only 25% of patients starting HD had PD even mentioned as an option. However, when patients were apprised of all treatment options, the percentage starting PD was higher than the national average. Quite often the patients are not given the choice and the physician makes the choice *(Wuerth et al. 2002).* In the UK, when given the free choice of therapy with proper patient education, the initial choice of therapy was 55:45 HD versus PD *(Little et al. 2001).* A recent US multivariate analysis in 4025 patients (1996-7) showed that selection of PD over HD was associated with lower age, white race and fewer co-morbid conditions. There was greater use of PD in employed, married, the autonomous and educated. Earlier referral (>4mths) had greater PD use *(Stack 2002).* Time of referral is another important determinant of modality choice. Patients that are referred late are more likely to go on to HD and remain on it *(Lameire et al. 1997).*

There is some evidence that using peritoneal dialysis initially preserves residual renal function *(Lysaght et al. 1991)*, produces better outcomes post renal transplant *(Bleyer et al.*

1999; Lambert et al. 1996) and reduces infection risks of blood bourne viruses *(Pereira and Levy 1997).*

Peritoneal dialysis is also significantly cheaper than haemodialysis. The Renal Review in 1994, estimated the cost to be £17,520 per patient per annum for PD, £23,600 for home haemodialysis and £29,140 for hospital based haemodialysis.

Patients using PD have been found to have better outcomes in terms of haemoglobin and blood pressure control *(Faller and Lameire 1994; Mailloux and Levey 1998).* However, patients with using peritoneal dialysis have more morbidity. According to the USRDS, dialysis patients have the same number of admissions, but those on PD spend longer in hospital *(USRDS Annual Data Report 2004).* The CANUSA study found, by multifactorial analysis, an association between prolonged hospitalisation and low creatinine clearance.

The data from the literature suggest that PD and HD do not seem to differ in respect of mortality over the initial 4-5 years *(Gokal and Hutchison 2002).* The comparison is difficult to make as there has never been a large scale randomised study comparing the two modalities other than one from the NECOSAD study. A recent analysis of 38 patients (out of 718 approached to partake in the randomised study from the NECOSAD cohort in the Netherlands) 'randomised' to either therapy, showed a better survival in the PD patients at 5 years *(Korevaar et al. 2003).*

In addition a number of factors impact on outcomes, not least of which is co-morbidity and differences in patient characteristics at start *(Xue et al. 2002)* and non medical factors *(Nissenson et al. 1993).* These need to be adjusted for when making comparisons *(van Manen et al. 2002).*

Several analyses have been undertaken in comparing the outcomes on PD and HD. Nolph *(Nolph 1996)* analysed the relative risk of death on PD as compared to HD and, by and large, found that mortality risk was equal for HD and PD in the various studies reported. Analysis from the Canadian Organ Replacement Registry (CORR) on patients starting RRT between 1990-1994, showed that for incident patients, the survival with PD was better in the first two years of treatment compared to HD with subsequently no difference up to four years *(Fenton et al. 1997).* In addition it showed that there was a significantly lower risk of death in PD patients across all ages and diabetes; for ages 0-64

years the relative risk of death was 0.54 for non-diabetic PD patients (HD being 1) and 0.73 for diabetic patients. A further comparative analysis from 11 Canadian centres showed that the apparent survival advantage of PD patients was due to lower co-morbidity and a lower burden of acute onset end-stage disease at the inception of dialysis; survivals were otherwise equal *(Murphy et al. 2000)*. A very recent analysis on Medicare patients starting dialysis in 1995-2000 in the United States has been reported by Vonesh et al 2004 and substantiates an earlier report from Medicare *(Collins et al. 1994)*. Among the 178,693 (45%) patients with no baseline co-morbidity, adjusted mortality rates in non-diabetic patients were significantly higher on HD than on PD. Among diabetic patients with no co-morbidity, HD was associated with a higher risk of death among younger patients and a lower risk of death among older patients. Within the group of 220,247 (55%) patients with baseline co-morbidity, adjusted mortality rates were not different between HD and PD. The authors conclude that survival differences between HD and PD are not constant, but vary substantially according to the underlying cause of ESRD, age, and level of baseline co-morbidity *(Vonesh et al 2004)*. A recent analysis from the USRDS database shows that after adjustment for co-morbidity and other related factors, patients in the United States above the age of 67 years on PD had a higher risk of death, especially for the diabetic population *(Collins et al. 2002)*. A Danish registry report shows results similar to the CORR database. This study corrected for co-morbidity and transplant status and found that the relative risk of death was lower on PD compared to HD over the first 18 months – thereafter the risk was the same *(Heaf, Lokkegaard, and Madsen 2002)*. The NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) prospective cohort study shows no difference in survival at 2 years (76% for both HD and PD) *(Jager et al. 2001)*. Long term survival from single centre analysis shows no difference at 15 years between PD and HD patients *(Maiorca and Cancarini 1999)*. It seems from these analyses that there is a 'bimodal' distribution to survival with initial advantage in favour of PD over the first 2-4 years, which thereafter changes in the direction of HD. Why this should be so is not clear. It may be that PD patients have less co-morbidity at start of dialysis, as has been suggested by the CHOICE (Choices for Healthy Outcomes in Caring for End-Stage Renal Disease) study in the US *(Miskulin et al. 2002)* or better RRF and predialysis education. The long-term outcomes are worse in PD and this is almost certainly related to decline in RRF and membrane changes affecting UF and solute clearance.

1.3. Medical Management of ESRD

As explained earlier, the kidney plays a key role in maintenance of normal blood pressure, haemoglobin levels and bone metabolism. Therefore, in addition to providing solute and water clearance by dialysis, treatment for hypertension, anaemia and bone disease are crucial elements in the management of patients on dialysis.

1.3.1. Hypertension

Pathophysiology

High blood pressure (BP) is a well-described complication of chronic kidney disease. Its prevalence is approximately 80% in HD and 50% in PD patients *(Rocco et al. 1997)*. The pathophysiology of hypertension in renal disease is not fully understood. An important mechanism is thought to be the increased extracellular fluid and sodium retained by patients with ESRD, but it is not the only factor implicated *(de Leeuw 1994)*. Another important factor is an inappropriate persistence of peripheral vascular resistance, but the reason for this is unknown.

Treatment of hypertension consists of removing enough extracellular fluid by ultrafiltration (UF) to reduce the blood pressure to normal. In Tassin, in a population of 692 patients treated by a long, slow haemodialysis, only 2.5 % required antihypertensive medication 3 months after start of dialysis. In 90 patients who had been previously dialysed for more than 3 months with dialysis sessions of duration 5 h or less 46 (52%) needed antihypertensive therapy. Three months after having been switched to a 3 × 8 hour weekly schedule, antihypertensive medications could be stopped in all but one patient, with return of systolic and diastolic blood pressures to normal values *(Charra et al. 1994[a]; Charra 1994[b]; de Leeuw 1994)*. These results are dependant on long, slow dialysis sessions of approximately 8 hours 3 times a week, and in part a reflection of adequate sodium and fluid balance and achievement of dry weight (this is an estimate of the weight at which the patient has no extra extracellular fluid). Most in-centre haemodialysis units worldwide are unable to provide this length of dialysis for logistic, patient numbers and cost reasons. Therefore most haemodialysis patients get 4 hours 3 times a week. Rapid, aggressive ultrafiltration then becomes necessary to return the patients to their dry weight They are then exposed to the vicious circle of poor haemodynamic tolerance to rapid ultrafiltration which leads to symptomatic intradialytic hypotension; fluid and/or sodium supplementation then

becomes mandatory to relieve acute symptoms, resulting in post dialysis residual fluid overload and sustained hypertension requiring antihypertensive medication, which will favour the return of intradialytic hypotension during the next dialysis session.

In PD patients, BP is better managed initially, perhaps related to persisting RRF and good ultrafiltration, with decline in the use of antihypertensive medications in the first 2-4 years *(Faller et al 1994)*. Thereafter, hypertension becomes more difficult to control with the need for increased antihypertensive agents.

Impact of Hypertension on Outcomes

Several studies have shown a high prevalence of left ventricular hypertrophy (LVH) in patients with decreased GFR and patients beginning dialysis *(Levin et al. 1996)*. Hypertension has been shown to be independently associated with LVH *(Foley et al. 1996)*. A few studies have shown a relationship between higher systolic blood pressure and clinical cardiovascular disease events *(Foley et al. 1996; Jungers et al. 1997)*.

Left ventricular hypertrophy and congestive heart failure were both strongly associated with subsequent mortality. However, lower rather than higher blood pressure was associated with a higher risk of death. The association between level of blood pressure and mortality does not appear to be consistent, with a number of studies reporting either positive or negative associations *(Mailloux and Levey 1998)*. One recent study showed a bimodal distribution ("U-shaped" relationship) with excess risk in HD patients with normal or low blood pressure, as well as in patients with very high blood pressure *(Zager et al. 1998)*. It is likely that excess risk in patients with low blood pressure reflects confounding effects of underlying or pre-existing cardiovascular disease on mortality, while the true relationship of blood pressure to mortality is reflected in the excess risk in patients with very high blood pressure as in the general population.

Consensus panels in the UK and other countries have defined hypertension in adults as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg. The Renal Association recommended standard for blood pressure control is a pre-haemodialysis blood pressure of 140/90 mmHg, a post-haemodialysis blood pressure of 130/80 mmHg and less than 130/80 mmHg for peritoneal dialysis *(Renal Association 2002)*.

1.3.2. Anaemia

Background

The primary cause of anaemia in patients with renal failure is insufficient production of erythropoietin (EPO) by the diseased kidneys. As kidney function declines, the likelihood of anaemia associated with EPO deficiency increases because the diseased kidneys are unable to produce sufficient quantities of EPO. There is a wide range of haemoglobin levels for any degree of kidney dysfunction.

Erythropoietin

Recombinant human erythropoietin (rHuEPO) has been used in the treatment of the anaemia of chronic renal failure since 1986 *(Eschbach et al. 1987; Winearls et al. 1986).* No therapy has been shown to be as effective as EPO in the treatment of anaemia of chronic renal failure. The main side effects of EPO therapy are hypertension and increased thrombotic episodes. Hypertension is managed with fluid removal and antihypertensives, it is usually only necessary to withdraw EPO for severe hypertension resistant to standard treatment.

Iron is critical for haemoglobin synthesis. The serum iron and the percent transferrin saturation (TSAT) reflect the amount of iron immediately available for haemoglobin synthesis. The transferrin molecule contains two binding sites for transporting iron from iron storage sites to erythroid progenitor cells. A total iron saturation of 50% indicates that half of the binding sites are occupied by iron. Serum ferritin reflects total body iron stores.

In contrast to absolute iron deficiency, relative iron deficiency results when there is a need for a greater amount of iron to support hemoglobin synthesis than can be released from iron stores (reticuloendothelial cells). This situation, which can be caused by pharmacological stimulation of erythropoiesis by EPO, can occur in the presence of reasonable iron stores. As a result, the percent total iron saturation decreases to levels consistent with iron deficiency despite a normal or elevated serum ferritin *(Allegra, Mengozzi, and Vasile 1991; Eschbach et al. 1987; Fishbane and Lynn" 1995).* While no single value of total iron saturation or serum ferritin accurately discriminates between ESRD patients who are or are not relatively iron deficient, available data demonstrate that the lower the total iron saturation and the serum ferritin, the higher the likelihood that a

patient is iron deficient, and the higher the total iron saturation and the serum ferritin, the lower the likelihood that a patient is iron deficient *(Fishbane, Frei, and Maesaka[b] 1995 ; Macdougall et al. 1998).* Some workers have used percentage hypochromic red cells *(Macdougall 1998)* or serum transferring receptor levels *(Tonbul et al. 1998)* as an indication of relative iron deficency.

A definition of adequate iron stores for patients with chronic renal disease, proposed by NICE in 2006, is a serum ferritin level of 200 – 500 µg/l for haemodialysis patients (100 – 500 µg/l for non-HD patients) and either hypochromic red cells less than 6% or transferrin saturation (TSAT) of > 20% *(CG39 Anaemia management in chronic kidney disease: NICE guideline).*

Iron deficiency (absolute or relative) has been shown to be present in as many as 25% to 37.5% of patients presenting with the anaemia of chronic renal disease and, if treated, can at least temporarily improve or correct the anaemia *(Hutchinson and Jones 1997; Silverberg et al. 1996).* Iron deficiency was the commonest cause for EPO resistance in ESRD, but this situation has improved by iron replacement strategies *(UK Renal Rigistry. The Eighth Annual Report. 2005).*

Impact of anaemia on outcomes

Anaemia is defined in terms of the haemoglobin or haematocrit below the normal levels in healthy adults of 11.5-16.5 g/dl or 37%-47% in women and 13.0-18.0 g/dl or 40%-50% in men.

Survival of dialysis patients declines as the haematocrit decreases below a range of 30% to 33% *(Foley et al. 1996).* Whereas one study failed to note any improved survival at a haemoglobin >11 g/dl compared to an haemoglobin 10 to 11 g/dl *(Madore et al. 1997),* several other reports have shown improved survival at higher haemoglobin/haematocrit levels. Survival was improved in Italian haemodialysis patients when the haematocrit exceeded 32%, either spontaneously or following EPO therapy, when compared to haematocrit <32% *(Locatelli, Conte, and Marcelli 1998)* and in the United States an haematocrit of 33% to 36% reduced the risk of death from any cause by 10% when compared to patients whose mean haematocrit was 30% to 33% *(Xia et al. 1999).*

Survival has been noted in one study to be better in patients with cardiac disease who attained and maintained a normal haematocrit compared to similar patients who did not attain and maintain a normal haematocrit. In fact, within both the normal haematocrit group and the control group, the mortality decreased at higher haematocrit levels. In those 200 patients who achieved and maintained a normal haematocrit for 6 months, mortality decreased to approximately 15% per year, versus 40% per year in those maintained at a haematocrit of 30%. There were no convincing factors that appeared to explain why those patients that did not achieve and stabilise at a normal haematocrit had a greater incidence of non-fatal myocardial infarctions or death than did the control group. A study that involved more than 1,200 haemodialysis patients with documented heart disease was discontinued when it appeared that those patients randomised to a target haematocrit in the normal range (42% ± 3%) were experiencing a greater incidence (30%, with a confidence interval of 0.9 to 1.9) of non-fatal myocardial infarctions or death than did the control group randomised to a target haematocrit of 30% ± 3%. The difference was not statistically significant at the time the study was terminated however *(Besarab et al. 1998).*

Left ventricular hypertrophy (LVH) is more likely in patients with anaemia *(Greaves et al. 1994; London et al. 1987)* and in patients with ESRD *(Silberberg et al[a]. 1989)*; in such patients the risk of death is increased 2.9-fold *(Silberberg[b] et al. 1989).* Partial correction of anaemia (haemoglobin 6.3 ± 0.8 to 11.4 ± 1.5 g/dl) with EPO resulted in partial regression of LVH in dialysis-dependent patients *(Silberberg et al. 1990).*

Quality of life either is not improved, or improved only slightly, when the haemoglobin is increased from 8 g/dl to a level no higher than 9 to 10 g/dl *(Ifudu et al. 1994; Levin, Lazarus, and Nissenson 1993).* However, quality of life of dialysis patients, as assessed by standardised patient questionnaires, increases as the haemoglobin increases above 10 to >12 g/dl *(Auer et al. 1992; Valderrabano 1996; Walls 1995).* Several studies have demonstrated that a normal haemoglobin/haematocrit is associated with better physical performance *(McMahon et al. 1999)*, better cognitive function *(Pickett et al.1999)*, improved brain oxygen supply *(Metry et al. 1999)*, and improved sleep patterns compared to lower haemoglobin/haematocrit levels *(Benz et al. 1999).* In a meta-analysis of 16 published studies assessing the impact of EPO on clinical end-points, there was substantial benefits on quality of life, hospitalisation rates and requirements for transfusion when haemoglobin rose from <8g/dl to >11g/dl *(Jones et al. 2004).* Based on these studies the Renal Association recommends a minimum level of haemoglobin of 10g/dl for adults with ESRD *(Renal Association 2002).*

1.3.3. Abnormalities of calcium, phosphorus and parathormone

Renal Osteodystrophy

Chronic kidney disease is associated with a variety of bone problems related to abnormalities in the metabolism of calcium, phosphorus, parathormone (PTH) and vitamin D. The major disorders of bone can be classified into those associated with high PTH levels (high bone turnover -osteitis fibrosa cystica) and those with low or normal PTH levels (low bone turnover - adynamic bone disease or osteomalacia). The hallmark lesion of chronic kidney disease is osteitis fibrosa, due to secondary hyperparathyroidism. However, with the advent of intensive treatments for secondary hyperparathyroidism, the prevalence of disorders associated with low or normal PTH levels has increased.

The Renal Association recommends that PTH levels should be less than 4 times the upper limit of normal, as per local laboratory assays *(Renal Association 2002).*

Extraosseus calcification of tissues

In addition to abnormalities in bone metabolism, abnormal calcium-phosphorus metabolism may lead to calciphylaxis or extraosseous calcification of soft tissues and blood vessels. This complication in its full manifestation has been reported to affect approximately 1% of dialysis patients *(Budisavljevic, Cheek, and Ploth 1996).*

However, in studies of coronary artery calcification using electron beam computed tomography, dialysis patients had coronary calcification scores that were several-fold higher than those of patients with known coronary artery disease *(Braun et al. 1996).* The pathogenesis remains unclear, but hyperphosphatemia, hypercalcemia, elevated calcium-phosphorus product, and increased PTH levels are probable contributors.

Impact of abnormalities of phosphate and calcium on outcomes.

Lowrie and Lew found a U-shaped relationship between mortality and serum phosphate level *(Lowrie and Lew 1992).* Elevated phosphorus and calcium-phosphorus product has been linked to increased mortality among patients on dialysis *(Block and Port 2000).* Block et al 1998 showed a higher mortality in patients with a serum phosphate greater than 2.1 mmol/l. The Renal Association recommends a phosphate level of less than 1.8 mmol/l, which is consistent with current evidence linked to mortality and not too low to be

unachievable *(Renal Association 2002)*. Severe hypercalcaemia (>3.0 mmol/l) was shown to be associated with higher mortality *(Lowrie and Lew 1992)*. Another study showed that hypocalcaemia was associated with ischaemic heart disease *(Foley et al. 1996)*. This has led to the Renal Association recommendation that serum calcium should be maintained between 2.2 – 2.6 mmol/l *(Renal Association 2002)*.

1.4. Provision of Renal Replacement Therapy

In 1978 the Office of Health Economics reviewed renal failure in the UK, which led to the Department of Health setting a target of 40 per million population for acceptance onto renal replacement therapy by 1987 *(Renal Failure: a Priority in Health?; End Stage Renal Failure [OHE Briefing No.11] 1980).*

In 1991 the Renal Association, in conjunction with the Royal College of Physicians, published a report detailing the projected needs of renal services to relieve the congestion in dialysis facilities and so improve acceptance and prevalence rates. The recommendations were based on two main studies and suggested a minimum acceptance rate of 80 per million population *(Feest et al. 1990; McGeown 1990).* These studies did not take into account the higher prevalence in ethnic minorities and elderly patients above 80 years of age. Later research suggested that this target was too low. End stage renal disease is 3-4 times more common in patients from an Asian and Afro-Caribbean background *(Department of Health. Report of an independent review of specialist services in London. 1993; Department of Health. Renal Purchasing Guidelines.London, 1996.; Raleigh 1997; Roderick et al. 1996)* and data from the 1998 Renal Review and UK Renal Registry that showed the acceptance rate in Wales was 128 per million population and Scotland was 108 per million population (areas with relatively less of the population from ethnic minorities) and in England was 92 per million population. In addition the Renal Association, 2002, and National Service Framework, 2003, stipulate that age should not be barrier to receiving renal replacement therapy. There is no official target set as yet but the Renal Association, in the 3rd edition of the report of the Standards Subcommittee 2002, states *"While it is difficult to be precise about the level of national need for RRT, a realistic figure is an acceptance rate of at least 120-130 pmp. It is likely that a minimum level of 100 pmp would apply to all health authorities".* The latest Renal Review shows that the annual acceptance rate was 101 pmp in the UK (98 pmp in England, 118 in Wales, 120 in Scotland and 109 in N. Ireland) *(UK Renal Registry. Sixth Annual Report 2003).* This shows there is an unmet need for renal replacement therapy, especially in England.

Also accounted for in the recommendations of this report was research showing that the further patients lived from a renal unit the less likely they were to receive renal replacement therapy *(Dalziel and Garrett 1987; Roderick et al. 1999).* Satellite units, providing mainly haemodialysis facilities were recommended as one solution to this problem. There were four National Renal Reviews commissioned by the Department of Health to ensure equity

of access to renal replacement therapy and plan future renal services *(Department of Health. Report of an independent review of specialist services in London.1993; Department of Health Renal Purchasing Guidelines.London, 1996; UK Renal Registry. Third Annual Report 2000 & Sixth Annual Report 2003).*

1.4.1. Factors affecting renal service provision

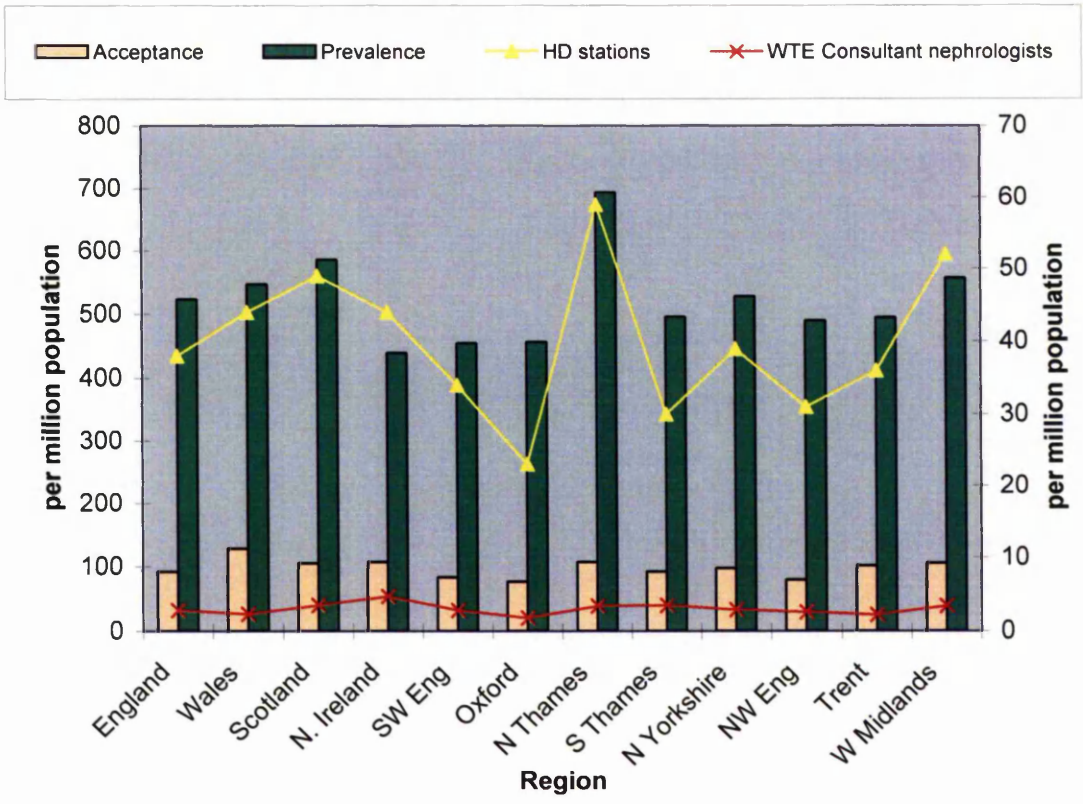
In the 1998 and 2002 UK Renal Survey a questionnaire was sent out to ask which factors had prevented local renal services from providing a complete service. The replies fall into 2 broad categories; i.e. lack of funding and resources and lack of staff. Lack of enough staff has become a bigger problem in the latest review *(UK Renal Registry. Third Annual Report 2000 & Sixth Annual Report 2003).*

Health care in the UK is provided through the National Health Service, designed by Lord Beveridge in 1942, and implemented in 1948. It is a public system, under government control, where funding is provided by taxation and is free to all the population. Healthcare competes with other sources of public spending priorities and a set budget is provided each year.

Renal replacement therapy is expensive and in 1998 was found to consume 2% of the NHS budget, despite renal patients only forming 0.2% of the NHS patient population. These costs were predicted to rise to 3% over the next 5 years *(UK Renal Registry. First Annual Report. 1998).* Resources are not unlimited, therefore the budget allocation to renal services must be 'rationed'. Rationing in the NHS is the process whereby treatment is provided on the basis of the overall population instead of on the need of the individual patient. Other NHS departments also compete for funding and in different parts of the country, where different health priorities are perceived, there is differential funding of renal departments. The above funding dilemmas can lead to unequal provision of renal therapy, when different patient groups (e.g. the elderly) and people living in different geographical locations can receive poorer access to and delivery of healthcare.

The acceptance and prevalence rates in different regions, and the resources in terms of haemodialysis facilities and staff are shown in figure1.1. It clearly illustrates the disparity in resource available for the treatment of ESRD and the inequity of treatment that results.

Figure 1.1. Comparison of acceptance and prevalence rates in different regions (values on left sided x axis) and haemodialysis stations and whole time equivalent nephrology consultants per million population (values on right sided x axis).



1.5. Non-treatment factors influencing outcomes

1.5.1. Age and Co-morbidity

Chronic kidney disease is a disease of the elderly. Data from EDTA and UK Renal Registries shows that the age profile and prevalence of diabetes in patients accepted for RRT is changing, with 47% of patients being over 65 years of age in 1998 as opposed to 11% 15 years before then. It would be expected that the presence of other co-morbid conditions would also have increased, but information on this is limited. As yet the UK Renal Registry does not have full information about co-morbidity and neither does the ERA/EDTA registry.

The incidence of ESRD increases with age *(Feest et al. 1990)*. Although elderly people have more co-morbid illnesses, which means they may not be suitable for RRT, there is still significant unmet need in this population. This is reflected in data from the UK Renal

Registry 2000 which shows that the acceptance rate peaks in the 65-74 age group and then falls, contrary to the incidence of ESRD. Also there is marked, and statistically significant, variation in the median age of patients accepted onto RRT around the country. It is unclear whether this bias is because of non-referral of elderly patients to renal services or due to non acceptance by renal units.

Survival rates are poor in the elderly dialysis population. A single centre study in the UK found 1 year survival rates were 90.6%, 72.6% and 53.5% in dialysis patients aged less than 65 years, 65-74 years and greater than 75 years. 5 year survival rates were 61.4%, 18.8% and 2.4% across the same age groups. Patients aged over 75 years spent 20% of their survival time in hospital *(Munshi et al. 2001)*.

Co-morbid conditions have a large impact on patient outcomes. In particular, diabetes, heart disease and peripheral vascular disease are major predictors of mortality *(Barrett et al. 1997; Lamping et al. 2000)*. A large proportion of patients with ESRD have these co-morbid conditions *(Metcalfe et al. 2000)* and, as the age of patients accepted for ESRD increases, it is likely that this proportion will remain high.

The optimal method for combining co-morbidity data to allow adequate case-mix analysis of outcomes for ESRD patients remains unclear. The first National Renal Review classified patients in the UK into low, medium and high risk according to age and diagnosis of diabetic nephropathy; median survival being 14.2, 7.4, and 3.5 years respectively. This classification did not take into account the impact of other co-morbid illnesses, in particular vascular disease, which had a high incidence in patients with ESRD and a significant impact on mortality *(Wright 1991)*.

Another index, based on age and co-morbidity, was proposed based on research done by Wright et al. in the US and modified by Khan et al in Scotland *(Khan et al. 1998)*.

This classification was used in a prospective study measuring mortality by 90 days after starting RRT *(Metcalfe et al. 2000)*. It was done in Scotland, but found a higher prevalence of medium and high risk groups in the ESRD population. This possibly reflects the difficulty with accurate data collection in retrospective studies.

A further study in 1999 *(Chandna et al. 1999)* assessed age, co-morbidity and functional status as predictors of mortality. They used a more complex co-morbidity scoring system

giving points for severity and number of co-morbidities, but did not include age in their index. They also found that there was no difference in survival in patients with diabetes and that severity of co-morbidity correlated better with survival than number of co-morbid conditions. These results would appear to make the previous 2 co-morbidity indices look unattractive. However this index has not been applied in a prospective study, and, as alluded to previously, retrospective data collection may underestimate severity and presence of co-morbidity. In addition grading the severity of co-morbid conditions was subjective and may not be reproducible. This study also showed a link between co-morbidity and hospitalisation.

Recently the Charlson Index *(Charlson et al. 1987; Charlson et al. 1994)*, used in a prospective study from Scotland, was also found to be predictive of mortality *(Metcalfe et al. 2000)*. This index has a more comprehensive list of co-morbidities than the previous indices.

However, other authors suggest individual co-morbidity is more predictive of outcome than co-morbidity indices *(van Manen et al. 2002)*. The UK Renal Registry has been collecting co-morbidity data since its inception, but data collection has been incomplete. The Tenth Annual Report of UK Renal Registry states only 9 centres in the UK have submitted sufficient data to allow inclusion of co-morbid illnesses in survival analyses. Results show that co-morbidity has a greater impact on survival in patients younger than 65 years. The co-morbid conditions most strongly predicting mortality were malignancy, ischaemic/neuropathic ulcers, liver disease, previous myocardial infarction and diabetes. *(UK Renal Registry.The Tenth Annual Report. 2007)*

1.5.2. Functional Status and Quality of Life

There has been a link established between mortality and patient function prior to and at inception of dialysis. The Karnofsky score was used to define patients into dependant, requiring assistance and normal function. This was an independent predictor of mortality when assessed 3 months prior to and at the inception of dialysis *(Chandna et al. 1999)*.Various health-related quality of life (HRQL) parameters are impacted on by dialysis treatment and its complications and meta analysis of quality of life studies suggest that perceived HRQL is better maintained on PD than HD *(Cameron et al. 2000)*. What is of striking relevance is that quality of life at start of dialysis therapy predicts outcome. Several studies show this *(DeOreo 1997; Mapes et al. 2004; Merkus et al. 2000)*.

1.5.3. Timing of referral to Renal Services

Referral to renal services may be defined as delayed when *"management could have been improved by earlier contact with renal services" (Eadington 1996).*

Some patients with ESRD will always present late as their renal disease may have developed quickly. A study from the USA estimated that 12% of patients who needed dialysis within 4 months of seeing a nephrologist had acute renal failure that progressed to ESRD, in them late referral was unavoidable *(Arora et al. 1999).* However a study in the UK showed that 50% of ESRD patients had documented results consistent with chronic renal failure greater than 8 weeks prior to referral, and 40% greater than 26 weeks prior to referral *(Ellis et al. 1998).*

Some studies have not found any association between age, gender, ethnicity, socioeconomic status, primary renal diagnosis, co-morbidity and late referral *(Arora et al. 1999; Sesso and Yoshihiro 1997).* Several studies used results from databases to identify patients with high serum creatinine indicative of advanced renal disease and then assessed whether they had been referred to a nephrologist. Two such studies in the USA found that age, non-white ethnicity and no medical insurance led to delayed referral*(Arora et al. 1999; Ifudu et al. 1999).* In the UK age and co-existing co-morbid illnesses were found to be significant factors for non-referral. Using the Wright/Khan Index for age and co-morbidity, in patients who had a serum creatinine greater than 500 μmol/l, 100% of low risk, 88% of medium risk and 37% of high risk patients were referred to a nephrologist *(Khan et al. 1994).*

There is no universal definition of late referral; thus different studies have defined it at different time intervals. In most studies of patients with ESRD, this has been calculated as the time interval between referral and initiation of dialysis. A survey of 14 different European centres found that there was wide geographical variation in the proportion of patients at individual centres who started dialysis within 1 month of seeing a nephrologist, from 10% in Brescia to 51% in Brussels. This variation was also seen in units in the same country, Leicester 16% and Manchester 38% *(Lameire et al. 1997).* Patients who are referred late are likely to start haemodialysis with venous catheters as access *(Arora et al. 1999; Sesso and Yoshihiro 1997)* and stay on haemodialysis *(Lameire et al. 1997).* They have also been found to have lower GFR, serum albumin, calcium and haemoglobin and higher serum

creatinine and phosphate at inception of dialysis than patients referred early *(Arora et al. 1999; Sesso and Yoshibiro 1997).*

Innes et al did find lower survival rates in patients referred late *(Innes et al. 1992).* Univariate analyses found a 2.8 higher risk of mortality in patients referred less than 1 month to a nephrologist, which was not significant on multivariate analysis where age, co-morbidity and serum albumin were independent predictors of mortality *(Sesso and Belasco 1996).* Ellis et al 1998, found no difference in mortality in patients who had been referred less or greater than 3 months. A recent retrospective study in the US found that patients who were seen consistently by nephrologists, in the 6 months immediately prior to initiation of dialysis, had a survival advantage once dialysis was started *(Khan et al 2005).*

Initially the Renal Association recommended referring all adults with a creatinine of greater than 150 μmol/l to a nephrologist *(Renal Association 1997).* However, as the importance of early referral has been recognized, new guidelines for referral of adults with chronic kidney disease (CKD), using laboratory calculated GFR, have been published by the Renal Association *(Renal Association 2002)* and in the Renal NSF *(National service framework for renal services 2003).*

1.5.4. Ethnicity

In the UK it has been found that Black and Asian people have a 3 fold higher relative risk of developing ESRD than the white population *(Lightstone et al.1995; Roderick et al.1996).* These relative risk increases with age *(Roderick et al. 1996).* Diabetes and hypertension are more prevalent in the Black and Asian population *(UK Prospective Diabetes Study (UKPDS) 1994; Balarajan 1995).* Diabetic nephropathy leading to ESRD is also more prevalent in Asians *(Burden et al. 1992)* and Afro-Caribbeans *(Roderick et al. 1994)* living in the UK. Several studies have shown a higher incidence of ESRD in American-Africans. This effect is exaggerated in older age groups. Diabetic nephropathy and hypertension occur in 3:1 and 7:1 respectively in American-Africans *(USRDS research studies 1991; Byrne, Nedelman, and Luke 1994; Rostand et al. 1982).*

Studies in the USA have shown that black Americans have a better survival than white patients on dialysis *(Pugh, Tuley, and Basu. 1994).* A review of incident dialysis patients in West London found comparable survival rates between white patients and those from ethnic minority groups *(Prasad et al 2004).*

1.5.5. Socio-economic status

Mortality and morbidity are affected adversely by social deprivation *(Marmot et al.. 1991; Wilkinson 1997).* Social deprivation is difficult to quantify and several deprivation indices have been developed to allow health services research *(Morris and Carstairs 1991).* The Carstairs deprivation index is based on 4 consensus variables: overcrowding, unemployment among men, social class and not owning a car. These are combined (by means of the Z score technique) to give a score for each postcode sector. These were then defined into quintiles. This technique was found to correlate well with standardised mortality ratios and long-term sickness *(Carstairs and Morris 1989).* The Townsend score is based on the total unemployment, number of no car households, house overcrowding and number of non-owner occupied households, using data from the 2001 census. The UK Registry has used this deprivation index to study the effects of socioeconomic status in the UK *(UK Renal Registry. Sixth Annual Report 2003).* Both indexes performed well in a comparison with other deprivation indices *(Morris and Carstairs 1991).*

Studies have shown that social deprivation (using the Carstairs index) in patients receiving RRT was the same as that in the general population *(Khan et al. 1993; Metcalfe et al. 1999).* The UK Registry found that social deprivation (using the Townsend Index) was associated with younger age, more co-morbidity and affected modality therapy *(UK Renal Registry. Sixth Annual Report. 2003).*

In the USA studies have shown that the incidence of ESRD is inversely related to socioeconomic status. A large study, in 1990, which recruited 9,390 patients found that there was an inverse correlation with socioeconomic status (calculated from postcodes) and incidence of ESRD in white Americans, but there was no association seen in American-Africans *(Byrne, Nedelman, and Luke. 1994).* However another large study, done in 1975, with 332,544 men did find an inverse correlation with socioeconomic status (calculated from postal codes) and incidence of ESRD in African-Americans, as well as whites *(Klag et al. 1997).* In the UK it has been found that socially deprived patients were more likely to be referred late; they were less likely to receive peritoneal dialysis (25.1 vs 34.8% on day 1, $p<0.0001$) or a renal transplant (5.3 vs 12.4% at 1 year, $p<0.0001$), and were less likely to attain UK Renal Association standards for hemoglobin and phosphate at 1 year. After adjusting for baseline co-morbidity, social deprivation was not associated with poorer survival *(Caskey et al. 2006)*

1.6. Improving outcomes

1.6.1. NHS/Renal Association priorities

Authorities responsible for the provision of renal services have stipulated that quality of care, with particular reference to patient outcomes, should be a priority when providing treatment for ESRD; it should also include cost-effectiveness, but this should not be the primary outcome *(Morbidity and mortality of dialysis. NIH Consensus Statement 1994; Renal Association 2002).*

In the UK, to promote this concept of quality of care the Renal Association set up a Standards Subcommittee to produce guidelines to set goals for treatment in order to improve outcomes using evidence-based recommendations and targets. It was also the aim to use these targets to address differences in outcome within the different demographic groups as well as geographical variations (national audit tool). To accomplish this, there was a need for a national registry. In 1995 a pilot project was started to collect data and form a registry to provide clinical and comparative audit to promote quality assurance programs in renal units across the country, using these guidelines and audit measures. In 1997 the UK Renal Registry moved to Bristol and produced its first annual report in 1998 *(UK Renal Registry).*

The concept of evidence-based medicine was to be the basis for improving care and outcomes. Its incorporation into medicine is, however, recent. In 1997 the Government announced reforms of the NHS and central to these was the commitment to provide quality health care services accessible to all the population *(Department of Health. White paper 1997).* The quality of services would be based on patient outcomes. Cost-effectiveness would also be part of the quality commitment, so that treatments recommended to improve outcomes would also be the most cost efficient. The National Institute of Clinical Excellence (NICE) was set up to "promote clinical and cost-effectiveness through guidance and audit, to support frontline staff. It will advise on the best practice in the use of existing treatment options, appraise new health interventions and advise the NHS on how they can be implemented and how best these might fit alongside existing treatments". The Government also announced the development of National Service Frameworks (NSF) which *"will set evidence-based standards and define service models for a specific service, put in place programs to support implementation and establish performance measures against which progress within an agreed timescale will be measured" (Department of Health).* NICE have so far published 1 appraisal

relevant to HD *"(1) that patients with end-stage kidney failure, who are suitable for home dialysis should be offered the choice between receiving their haemodialysis at home or in a hospital/satellite unit; no matter where they live in England and Wales*

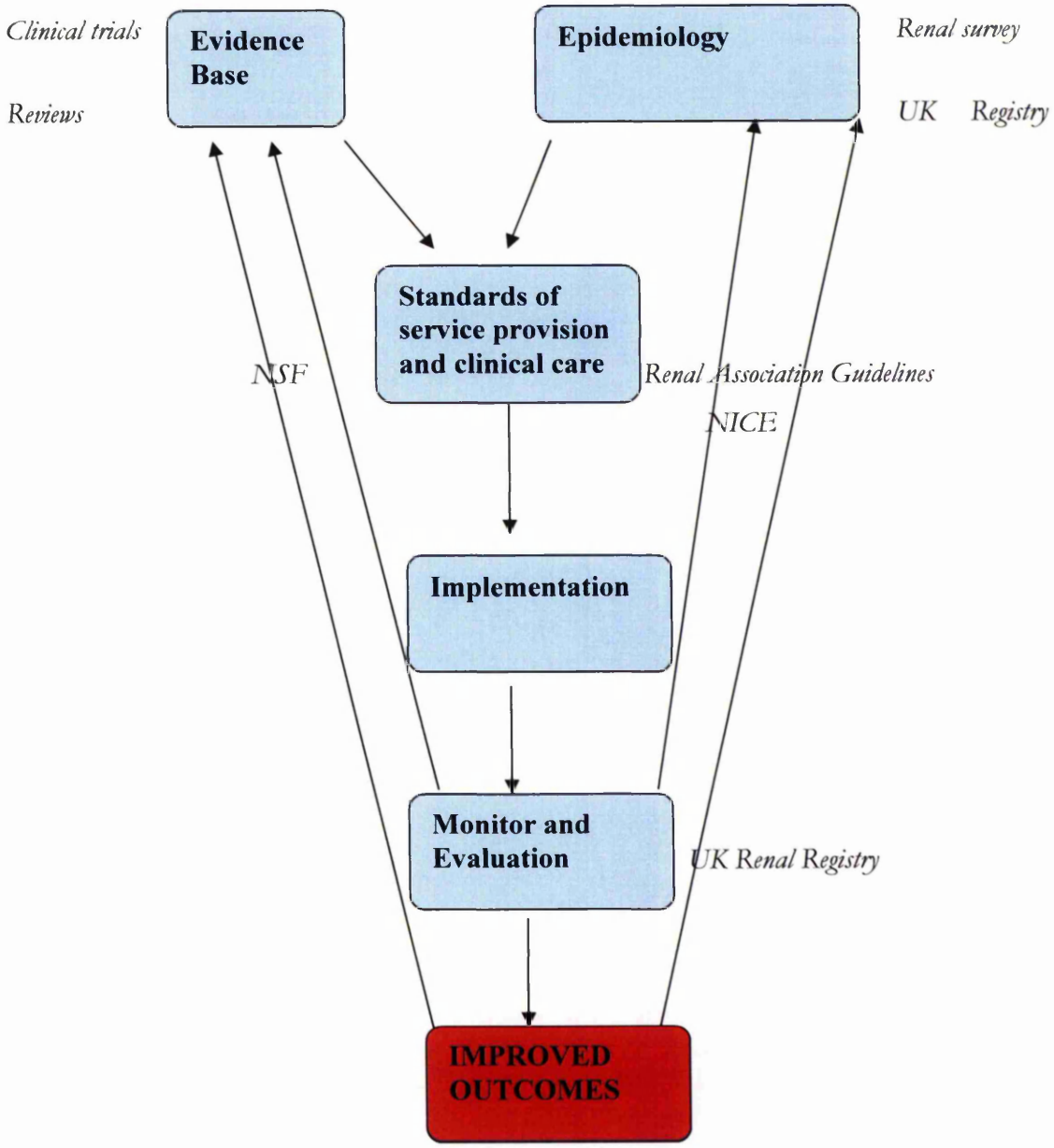
The recently published Renal NSF has set the bench mark for developments and provision for renal services over the next decade. It recommends 5 standards for the delivery of RRT, as shown in table 1.5.

Table 1.6. Standards in the Renal National Service Framework*(National service framework for renal services).*

Standard one: A patient-centred service
All children, young people and adults with chronic kidney disease are to have access to information that enables them with their carers to make informed decisions and encourages partnership in decision making, with an agreed care plan that supports them in managing their condition to achieve the best possible quality of life.
Standard two: Preparation and choice
All children, young people and adults approaching established renal failure are to receive timely preparation for renal replacement therapy so the complications and progression of their disease are minimised, and their choice of clinically appropriate treatment options is maximised.
Standard three: Elective dialysis access surgery
All children, young people and adults with established renal failure are to have timely and appropriate surgery for permanent vascular or peritoneal dialysis access, which is monitored and maintained to achieve its maximum longevity.
Standard four: Dialysis
Renal services are to ensure the delivery of high quality clinically appropriate forms of dialysis which are designed around individual needs and preferences and are available to patients of all ages throughout their lives.
Standard five: Transplantation
All children, young people and adults likely to benefit from a kidney transplant are to receive a high quality service which supports them in managing their transplant and enables them to achieve the best possible quality of life.

The first 4 standards are very pertinent to this study. For correct implementation of the strategy and vision of the Renal NSF, a schema of approach and care is needed. One such overview of care if depicted in figure 1.2, which outlines the need for an evidence base (derived from trials and reviews to set standards of care and infrastructure needed for provision of care) and epidemiology of renal disease (to provide the audit arm for implementation and assess outcomes). The implementation of standards need monitoring, and any deficit in care in achieving standards of care needs to be rectified; this may need both increased resource and quality of care.

Figure 1.2. Concept of quality assurance in the ESRD treatment program



1.6.2. Evidence based medicine

Since the 1960's it has been accepted by the medical profession, and by the Department of Health, that results of well-designed trials should form the basis of the treatment of patients with disease. This concept is termed "evidence-based medicine" and is defined as *"the process of systematically reviewing, appraising and using clinical research findings to answer a specific question, so helping in the delivery of optimum clinical care to patients" (Rosenberg and Donald 1995).*

The best type of study giving the most robust conclusions is the randomised, control trial. This is because randomisation of an adequate number of subjects allows both known and unknown confounding factors to be considered *(Oxman, Sackett, and Guyatt 1993).* Unfortunately, when the disease under study is relatively uncommon, the numbers required for a randomised control trial may be prohibitively huge. For example, the prevalence of cardiovascular disease is approximately 700,000 per million population in England compared with the prevalence of ESRD of 554 per million population in England. Listed on PUBMED by July 2006, there have been 17,664 randomised, control trials in heart disease and 3,924 in renal disease, of which 1,395 were in end stage renal disease. Also, randomised control trials are sometimes not valid for ethical reasons. Prospective, cohort studies can then be used to provide medical evidence, if randomised control trials cannot be undertaken. Unlike randomised, control trials only known confounding factors can be accounted for in the analysis of results of these studies. Case-control studies are useful when the condition is rare. Retrospective studies are the cheapest and the easiest to perform, but unequal medical surveillance and recall between the groups of people with the outcome of interest can lead to serious errors of bias. These errors become more important if the difference in the study outcome is small between the 2 groups *(Jaeschke, Guyatt, and Sackett. 1994).*

To inform their medical practice individual practitioners can do a critical appraisal of the medical literature. There are now large medical databases, which allow easy access to the medical literature, for example PUBMED provided by the US National Institute for Health. In 1979, Archie Cochrane stated *"it is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all the relevant randomised control trials."* From this concept arose the Cochrane Library in 1995, a collection

of databases that contain systematic reviews and appraisals of the medical literature, and produces clinical guidelines based on this. It has also come to include other databases performing systematic reviews. The main advantage with these reviews is that they have a rigorous methodology to perform literature reviews, which takes into account only high quality, large randomised control trials, and their reviews are not commercially funded.

1.6.3. Standards and Guidelines

Guidelines based on systematic reviews (as described above) are scientifically robust and should be disseminated to all relevant health professionals and patients. Unfortunately the lack of enough well designed trials means that these guidelines will only cover some aspects of the treatment of ESRD. So in 1990 the Executive Committee of the Renal Association formed a Subcommittee, the Standards and Audit Subcommittee, charged with producing a consensus statement of recommended standards and good practice for the treatment of renal failure. Their intent was to produce guidelines and recommendations for all aspects of ESRD management, clearly outlining the scientific evidence behind each recommendation, suggesting areas for further research and setting quantitative measures for audit. The first edition was produced in April 1995, the second in November 1997 and a third edition in 2002.

Clinical guidelines can be defined as *"systematically developed statements designed to help practitioners decide on specific clinical conditions or circumstances" (Field and Lohr 1995).* However clinical judgment is required in applying these guidelines to individual cases *(Hurwitz 1999).* Therefore, guidelines should provide information on the strength of evidence they are based upon with regard to the benefit to a defined group of patients and not be completely inflexible. The guidelines produced by the Renal Association are based on the grading of the US Department of Health and Human Services and are shown in table 1.6.

Table 1.7. Categories of strength used in guideline statements

Strength of evidence *(Woolf et al. 1990)*	
Ia	Evidence from meta-analysis of randomised control trials
Ib	Evidence from 1 randomised control trial
IIa	Evidence from at least one control trial without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from descriptive studies, i.e. comparative studies, correlation studies and case-controlled studies
IV	Evidence from expert committee reports or opinions of respected authorities
Strength of recommendation *(Renal Association 1997)*	
A	Evidence from at least one properly performed randomised control trial (Ib) or meta-analysis of several control studies (Ia)
B	Well conducted clinical studies, but no randomised, control trials; evidence may be extensive but generally descriptive (IIa, IIb and III)
C	An absence of directly applicable studies of good quality (IV)

As well as suggesting the best treatment to improve patient outcomes, guidelines can also help services be cost effective, reducing the need for unnecessary treatments, and also helping to plan the future resource allocation for health services so there are resources available for necessary, effective treatments. In renal services the Renal Association guidelines have been used by the Kidney Alliance to produce a document suggesting future delivery of renal services *(Kidney Alliance 2001).*

However, guidelines have a potential for harm if they are wrong. There are 3 main reasons why this may occur *(Woolf et al. 1999).* Firstly the scientific evidence may not be adequate, secondly expert opinion can be based upon personal experience and misconceptions *(Kane 1995)* and thirdly, patient needs may not be taken into consideration.

1.6.4. Implementing Guidelines

There have been some studies looking into the outcome of implementing DOQI guidelines in ESRD patients in the USA*(Bennett et al. 1997; DeOreo 1994; DeOreo and Eschbach 1999; Messana 1994; Messana 2001; VanValkenburgh and Snyder 1994).* Several found an improvement in overall achievement of standards*(Bennett et al. 1997; VanValkenburgh and Snyder 1994)*, one found a decrease in hospitalisation rates but not in mortality *(Bennett et al. 1997).* A recent, prospective study found that achieving the Renal Association standards for haemoglobin and albumin, but not urea reduction ratio for haemodialysis, were associated with better survival on dialysis *(Metcalfe et al. 2003).* Many barriers have been suggested to the implementation of these standards and improvement of outcomes. These range from lack of staff and staff training, lack of personnel to adequately monitor patient outcomes and the inability of units to provide the treatments the authors believe will improve patient outcomes, e.g. longer hours on dialysis.

1.7. Summary

The treatment of end stage renal disease is complex and many different factors combine to affect the outcomes of patients treated with renal replacement therapy. As the number, age and co-morbidity of patients on dialysis increases, the challenge as always is how to provide the optimum treatment within the confines of a finite allocation of NHS resource. The Renal Association guidelines for management of ESRD have begun to define targets and goals to improve outcomes, but the evidence is still lacking for many guidelines. It will not be possible to provide randomised, control evidence for many areas of management of ESRD. Therefore prospective, cohort studies studying outcomes are required to assess the impact of these standards. It is hoped that this study will provide some answers about methods to improve outcomes, and the place of the Renal Association standards, of "real-life" ESRD patients attending renal units in the UK.

Chapter 2: Aims

This study was undertaken to assess the factors that impact on outcome, including the achievement of national standards of care. The concept that evidence-based standards should form the basis of clinical care is not disputed. Whether implementation outside the trial 'environment' has an impact on outcomes remains an open issue. This project is therefore both a prospective audit of practice in a large cohort of ESRD patients starting dialysis in the North West of England and a study to assess the impact of clinical and socio-economic factors in outcome and whether standards affect this in a positive manner.

The study aims are:

1. To determine whether implementation of current national standards in relation to the achievement or non-achievement, improves outcomes in ESRD patients, receiving dialysis.

2. To assess the impact on outcomes in ESRD patients, receiving dialysis, of non-treatment factors (for example, ethnicity and socio-economic factors) at the start of dialysis treatment.

3. To assess the impact of mode of referral to nephrology services and dialysis modality, including haemodialysis access, on outcomes in patients with ESRD.

4. To report the strongest predictors of outcomes in terms of mortality, transplantation and hospitalisation in patients with ESRD, receiving dialysis.

Chapter 3: Patients and Methods

The study of implementation of renal standards (SIRS) was based at Manchester Royal Infirmary, a teaching hospital in the North West of England. I (AT), supported by 2 colleagues, Mrs. Jean Winterbottom (JW) and Mrs. Beverley Lane (BL), collected information on all incident ESRD patients who commenced renal replacement therapy, out of an overall general population of 4.5 million, encompassing Greater Manchester, Lancashire, parts of Cheshire and parts of Cumbria.

3.1 Contribution of Investigators

AT designed the ACCESS© database used to collect all the data. The data to be collected was decided at the beginning of the study, after discussion with the study steering group: Dr Robert Foley (Hope Hospital and later, Nephrology Analytical Services Centre USA), Dr Michael Venning (Withington Hospital, and later Manchester Royal Infirmary), Dr Robert Coward (Preston Royal Infirmary) and the principal supervisor, Professor Ram Gokal (Manchester Royal Infirmary). JW collected data at patient recruitment and BL collected patient follow up data by visiting all the main renal units weekly and the satellite units once a month. AT, JW and BL collected patient data into laptop computers, and informed and interviewed patients (in person or by telephone, depending on patient preference). Patients signed a consent form and were given a leaflet stating the purpose of the study and who to contact if they had any concerns. AT collated the information and produced individual patient forms, alerting individual renal units if patients were failing to achieve the renal association standards and which standards they were. AT entered responses on the returned forms into the database, which stated the reasons the unit staff felt patients were failing to achieve the renal association standards. AT interrogated the data, using different statistical methods, and presented the results via newsletters and presentations at local, regional, national and international meetings. The final data analyses, presented in this thesis, were done by AT in the research laboratory in Minneapolis, at the Nephrology Analytical Services Centre, where the USRDS database is analysed, under supervision of Dr R. Foley. The study also received invaluable support from the staff working in the renal units of the different centres.

3.2 Study design

This was a prospective, inception cohort study which recruited from 1st April 2000 until 31st March 2003; consecutive adults commencing RRT. There was detailed follow up for a maximum of 24 months. Mortality and transplantation was recorded for entire study duration, i.e. 3 years.

3.3 Setting

At the start of the study there were initially 4 main renal units (hubs) and their satellite units as outlined in table 3.1. With the re-configuration of the renal services in the Manchester conurbation (managed by the Greater Manchester Renal Network), Withington renal unit became part of the main unit at the Manchester Royal Infirmary. The catchment population covered by each of the 3 'hubs' then became roughly equal (1.5million each).

Table 3.1. Details of main renal units and their satellite dialysis facilities

Main Unit	Satellite Units
Manchester Royal Infirmary	North Manchester General Hospital. Wythenshawe Hospital (since closure of Withington renal unit on 1st September 2001). Macclesfield General Hospital (since closure of Withington renal unit on 1st September 2001).
Withington Hospital (closed 1st September 2001 and transferred to Manchester Royal Infirmary).	Macclesfield General Hospital (transferred to Manchester Royal Infirmary 1st September 2001). Leighton Hospital (transferred to North Staffordshire Royal Infirmary after closure of Withington renal unit on 1st September 2001, consequently this site became outside the geographical boundaries of this study after this date).
Hope Hospital, Salford.	Birch Hill Hospital, Rochdale.
Preston Royal Infirmary	Accrington and Victoria Hospital, Blackburn. Devonshire Road Hospital, Blackpool. Furness General Hospital, Barrow. Westmorland General Hospital, Kendal.

3.4 Subjects

Subjects were recruited from 1st April 2000 until 31st March 2003.

Inclusion criteria:

All adults who have new ESRD, defined by the Renal Association Standards Subcommittee *(Renal Association 2002)* as *"new patients who are accepted and transplanted or dialysed for more than 90 days or patients who are diagnosed with ESRD (i.e. accepted for dialysis in anticipation that they will need it indefinitely) and who die within 90 days or patients dialysed who are initially thought to have acute renal failure but are subsequently diagnosed as having ESRD."* The steering group also decided to include patients who had a previously functioning renal transplant, which had failed and patients then required dialysis. The rationale was that this group represents a significant proportion of patients starting dialysis and had not been specifically studied in any other similar cohort study. These patients were recorded as a separate group (see table 3.4).

Exit criteria:

- Patients who unexpectedly recovered function, i.e. became dialysis independent for longer than 90 days.
- Death
- Renal transplantation
- Migration away from geographical area under study

Ethical Approval:

The Ethics Research Committee felt that ethical approval was not required for this study as the drive to improve patient outcomes by monitoring and implementing national standards was part of clinical governance, which every NHS trust and department has a statutory obligation to provide. However, it was felt, by the steering group, that every patient should be informed that they were on the study and researchers were collecting their medical data and they should be allowed to refuse consent if they wished. No subjects refused consent.

3.5 Baseline data collection

The following data, from medical records, was collected into an ACCESS© database at the patient's local renal unit, at their time of entry into the study (prior to first dialysis session):

Demographic data

- Date of birth, gender, ethnicity and postcode

Primary renal diagnosis

- Recorded using ERA/EDTA diagnosis codes (See appendix 1).

Co-morbid illnesses

- Diabetes mellitus
- Myocardial infarction (separately noted if greater or less than three months prior to entry onto study)
- Angina and congestive cardiac failure (severity noted according to the New York Heart Association classification, shown in table 3.2.)
- Coronary artery bypass graft (CABG) or coronary angioplasty
- Peripheral vascular disease (severity graded using Society of Vascular Surgeons classification, shown in table 3.3)
- Ischaemic ulcers
- Amputation
- Peripheral angioplasty
- Cerebrovascular disease
- Dementia
- Hemiplegia
- Chronic obstructive pulmonary disease (COPD)
- Peptic ulcer disease
- Liver disease (other than viral hepatitis)
- Hepatitis B
- Hepatitis C
- Human immuno-deficiency virus (HIV)
- Lymphoma
- Leukaemia
- Solid tumour
- Connective tissues disorders
- Congenital abnormalities

Table 3.2. New York Heart Association grades for severity of heart disease

Grade	Symptoms
1	No symptoms from ordinary activities
2	Mild limitation of activity
3	Marked limitation of activity
4	Symptoms occur at rest

Table 3.3. Society of Vascular Surgeons grades for severity of peripheral vascular disease

Grade	Symptoms
1	No symptoms from ordinary activities
2	Symptoms of intermittent claudication
3	Ischaemic rest pain
4	Tissue loss due to ischaemia

Presentation to renal services

- Mode of presentation: a definition was agreed by the steering group, based on the definitions used by the ARMS study (a large prospective study of patients with ESRD based in Scotland. *Metcalfe et al. 2000*). This was based on timing between referral and dialysis (greater or less than 1 month), dialysis access at inception of dialysis (permanent, i.e. AV fistula or graft or Tenckhoff catheter, or semi-permanent/temporary, i.e. dialysis lines/catheters or rigid PD catheters) and speed of renal function decline (acute, chronic or acute-on-chronic). See table 3.4.
- Date of referral
- Serum creatinine at referral
- Who referral was made by (GP, hospital consultant, diabetic clinic, transfer from another hospital ward or accident and emergency department)
- Date of creatinine first noted to be greater than 150 μmol/l
- Date first seen by a nephrologist
- Serum creatinine when first seen by nephrologist

Table 3.4. Mode of presentation to renal services

Database field	Length of follow up by renal services, prior to start of RRT	Access	Rate of renal deterioration
Planned CRF	> 1 month	Permanent	Chronic
Unplanned CRF	> 1 month	Semi-permanent/ temporary	Chronic
Acute on chronic RF	> 1 month	Permanent or Semi-permanent/ temporary	Acute-on-chronic
Failed transplant[λ]	> 1 month	Permanent or Semi-permanent/ temporary	Chronic/Acute/ Acute-on-chronic
ESRF	< 1 month	Permanent or Semi-permanent/ temporary	Unknown
ARF	< 1 month	Permanent or Semi-permanent/ temporary	Acute
Lost to FU[κ]	< 1 month	Permanent or Semi-permanent/ temporary	Chronic or acute-on-chronic

[λ] ***patients were entered into this group if they were using a functioning renal transplant as RRT prior to starting dialysis***

[κ] ***patients were entered into this group when a letter from renal services was filed in the notes stating the patient had failed to attend for renal follow up***

Renal replacement therapy

- Date of inception of renal replacement therapy
- Mode of outpatient renal replacement therapy
- Mode of acute, inpatient dialysis
- Access was noted for acute and maintenance dialysis

Biochemical, anthropometric and treatment data

- Biochemical indices: serum sodium, potassium, urea, calcium, albumin, phosphate, bicarbonate, chloride, aluminium, cholesterol and parathormone
- Predialysis weight
- Blood pressure: systolic and diastolic
- Haematological indices: haemoglobin, ferritin, iron and total iron binding capacity (TIBC)
- Treatment: EPO (and the dose), statin and the number of antihypertensive medications

Hospital admission and discharge dates, during which dialysis was started

Calculated variables

- Townsend score: from the 2001 census a Townsend score was calculated for each postcode. The formula includes total unemployment, number of no car households, house overcrowding and the number of non-owner occupied households. The UK Renal Registry uses this deprivation score *(UK Renal Registry. Sixth Annual Report. 2003).*
- GFR at initiation of dialysis: this was calculated using the Cockcroft and Gault formula *(Cockcroft and Gault 1976)*, using sex, weight, age and serum creatinine.

3.6 Follow up data collection

- Subjects had detailed follow up for up to 24 months on dialysis at 3, 6, 9, 12, 18 and 24 months. Death and transplantation were noted continuously during study duration.
- The date and reason for leaving the study were noted if the subject did not reach their allotted follow up period
- For patients who died, the place and cause of death was also noted
- Their current co-morbid illnesses were noted in the identical manner to the baseline data collection definitions
- Admission and discharge dates, in the intervening time were noted, with a reason for each admission
- The procedures that were carried out were noted
- The numbers of episodes of peritonitis were noted, the organism responsible and the outcome of the episode
- Their current dialysis mode and access was noted and their dialysis prescription (i.e. dialyser, blood flow rate, duration of dialysis and sessions per week for haemodialysis; size and strength of peritoneal dialysis fluid and whether peritoneal dialysis was intermittent, automated or continuous ambulatory peritoneal dialysis).
- The adequacy of dialysis was noted, using the urea reduction ratio for haemodialysis and the urea kinetic model (Kt/V) for peritoneal dialysis. In addition, the transport status for the peritoneal membrane was noted in peritoneal dialysis patients
- If the mode of dialysis was different to that at baseline, this was also noted.
- Current serum biochemistry (serum sodium, potassium, urea, calcium, albumin, phosphate, bicarbonate, chloride, aluminum, cholesterol and parathormone), weight and blood pressure (pre and post dialysis session for HD patients) and haematological indices (haemoglobin, ferritin, iron and TIBC) were noted.
- Also recorded was whether the subject was prescribed erythropoietin (and the dose), a statin and the number of antihypertensive medications.

3.7 Patient interviews

Patients were interviewed by telephone or in person, depending on their preference, after discharge from hospital to ascertain whether they had been informed about the dialysis options available to them and whether they had been offered any choice regarding this. Social history in terms of marital status, smoking and drinking history was also taken at this time.

3.8 Standards selected for Implementation

The following standards were measured, as taken from the Renal Association Standards document in 1997:

1. Haemoglobin greater than 100 g/l
2. Blood pressure below 160/90 mmHg for subjects older than 60 years and below 140/90 for subjects younger than 60 years.
3. Corrected calcium between 2-2.65 mmol/l*, phosphate between 1-1.8 mmol/l, bicarbonate between 20-30 mmol/l and parathormone up to 200 pg/l.
4. Urea reduction ratio greater than 65% for patients on thrice weekly haemodialysis and greater than 80% for patients dialysing less frequently.
5. Kt/V of greater than 1.7 and less than 1 episode of peritonitis per 18 patient months for peritoneal dialysis.

**The measurement for calcium, corrected for albumin, is susceptible to problems of inter-assay variability and, in addition, there are several formulae in use for "correction" of albumin. For the purposes of this study, all participating centres and laboratories agreed that the Renal Association standard quoted above was appropriate for their patients with ESRD.*

In 2002, the Renal Association published an updated version of the 1997 standards document. The only standard affected in our study was the blood pressure standard; the new recommendations were a target blood pressure of less than 140/90 mmHg immediately pre haemodialysis session and 130/80 mmHg post session. The target blood pressure for peritoneal dialysis was less than 130/80 mmHg. This edition also recommended the use of arterio-venous fistula for the majority of patients on

haemodialysis (67% of incident patients known to nephrology services for > 3 months), which was incorporated into our study.

3.9 Methods of Implementation

For each of the above standards that failed to be met, a report was sent to the subject's local renal unit. A copy was given to a nominated staff member on the renal unit and a copy to the nominated consultant at each site. On the reverse of each form was a simple questionnaire to be filled in to explain why the standard could not be met. The responses were noted in the SIRS database. Results comparing individual unit performances and the region as a whole in comparison to the standards were presented at 6 local renal unit meetings, 5 regional audit meetings and 6 newsletters were sent to the principal staff on all the renal units on the study.

3.10 Data Analysis

Two statistical packages were used. SPSS© (version 11.0) was used at Manchester Royal Infirmary by AT. SAS and SPSS were used at the Nephrology Analytical Services Centre, Minneapolis (where USRDS data are analysed), where the data were analysed by AT under the supervision of Dr Robert Foley.

Chapter 4: Description of SIRS study population

This chapter describes the follow up and characteristics of the SIRS study population with reference to data from UK Renal Registry of patients with ESRD *(UK Renal Registry. Sixth Annual Report. 2003)* where appropriate.

4.1. Study recruitment and follow up

The date of first RRT, either dialysis session or date of transplant, was taken as the point of subject entry into the study. The date of first RRT, either dialysis session or date of transplant, was taken as the point of subject entry into the study. Except for patients returning to dialysis after failed kidney transplantation; for them date of entry is their first dialysis in the study dates. Table 4.1 shows the number of patients recruited during the course of the study.

Table 4.1. Number of patients entered by quarter per year, defining the time cohorts A – L of the study

	2000	2001	2002	2003
1st Quarter *(January – March)*	-	106 *(D)*	95 *(H)*	83 *(L)*
2nd Quarter *(April - June)*	88 *(A)*	97 *(E)*	105 *(I)*	-
3rd Quarter *(July - September)*	95 *(B)*	84 *(F)*	78 *(J)*	-
4th Quarter *(October - December)*	96 *(C)*	99 *(G)*	83 *(K)*	-

When patients started renal replacement therapy this became time = 0 for all of them, indicating the start of their follow up in the study. Table 4.2. shows when the groups of patients defined above were followed up.

Table 4.2. Subject entry and follow up during study, according to time cohorts A – L

		T=0	T=3 months	T=6 months	T=9 months	T=12 months	T=18 months	T=24 months
2000	2nd Quarter	A						
	3rd Quarter	B	A					
	4th Quarter	C	B	A				
2001	1st Quarter	D	C	B	A			
	2nd Quarter	E	D	C	B	A		
	3rd Quarter	F	E	D	C	B		
	4th Quarter	G	F	E	D	C	A	
2002	1st Quarter	H	G	F	E	D	B	
	2nd Quarter	I	H	G	F	E	C	A
	3rd Quarter	J	I	H	G	F	D	B
	4th Quarter	K	J	I	H	G	E	C
2003	1st Quarter	L	K	J	I	H	F	D

Figure 4.1. shows how many patients were followed up at 3, 6, 9, 12, 18 and 24 month intervals after their entry onto the study. The number of patients who exited from the study, and the reasons why, are also shown. There is a significant attrition rate in the percentage of the original cohort who remain on dialysis at different time points, reflecting transplantation and death, with the sharpest drop in the first 3 months of dialysis. Factors associated with mortality and transplantation are shown in chapter 10.

Figure 4.1. Number of patients recruited and followed up during study

4.2. Acceptance rates for RRT

Over the study period, April 2000-April 2003, 1109 patients were entered onto the SIRS database. The overall catchment population for the renal units where patients were recruited onto the study was 4.5 million *(Greater Manchester Renal Network).* The average acceptance rate for RRT was 82 per million population per year. Data from the UK registry shows that crude acceptance rates for other renal units in the UK in 2002 ranged between 52-164.9 pmp/year. The average acceptance rate for the UK was estimated to be 101 pmp/year for 2002. There will be some error in these acceptance rates because of the effect of cross boundary migration and the re-organisation of renal services during the course of this study, but on the assumption that this error is small, acceptance rates in the Northwest are lower than the average for the UK.

4.3. Characteristics of the SIRS study population at recruitment (time = 0)

Different characteristics of the study population are described in tables 4.3-4.10 below. This allows the SIRS population to be compared with different ESRD populations separated, for example, by time or distance. These tables also provide the basis for further analysis, by suggesting unusual characteristics warranting further investigation, which may affect the outcomes of these patients. The proportion of missing data were calculated, as characteristics with less than 90% data completion were either not used for further analysis, in subsequent chapters, or the analyses were interpreted with caution, as reporting errors were likely to be high.

Table 4.3. Demographic data (time = 0)

	Frequency (%)	Median (IQR)	Missing data (%)	*Data from UK Renal Registry*
Age (years)		60.8 (25.5)	0	*65.5*
Male gender	60.4		0	*61.8*
Ethnic Group			2.3	
White	87.1			*86*
Asian	9.4			*9*
Black	3.0			*4*
Chinese	0.5			*1*
Smoking Status			30.3	
Never	46.1			
Current	20.8			
Ex <5 years	10.8			
Ex >5 years	22.3			
Pack years		0 (16)	47	
Units of alcohol (per week)		0 (1)	35.8	
Marital Status			8.8	
Married	62.7			
Widowed	10.1			
Separated	1.4			
Single	19.6			
Divorced	4.4			
Co-habits	1.8			

Table 4.3. shows that the median age of the SIRS cohort is younger than the UK average. This suggests that there is a bias in acceptance of older patients for renal replacement therapy.

Table 4.4. Primary renal diagnosis (time = 0)

	Frequency (%)	Missing data (%)	*Data from UK Renal Registry*
Primary Renal Diagnosis		0	***11.4***
Glomerulonephritis	**15.7**		***9.8***
Interstitial nephritis	**21.3**		-
Renovascular	**6.9**		***7.0***
Diabetic nephropathy	**20.3**		***17.6***
Other multisystem	**11.4**		-
Unknown	**24.4**		***21.9***

Table 4.4 shows that the commonest single diagnosis causing ESRD was diabetic nephropathy and the second commonest renal diagnosis is renovascular disease. The proportion of patients whose underlying renal disease was unknown is higher than the UK average. These differences may occur because of the younger age of the SIRS population or differences in reporting and recording of data. Renal diagnosis is known to vary with age, for example the proportion of diabetic nephropathy causing ESRD in the UK population aged under 65 years is 20.4% and 14.5% in those aged over 65 years. This suggests that the higher proportion of diabetic nephropathy may reflect the relatively young age of the SIRS cohort. Both renovascular disease and unknown renal aetiology are commoner in older age groups *(UK Renal Registry. Sixth Annual Report. 2003).* 2.8% in age less than 65 years compared with 11.2% for those older than 65 years for renovascular disease and 17.5% compared with 26.5% respectively, for unknown aetiology. Therefore both these diagnoses appear to be more prevalent in the young SIRS cohort. It is noted, however, that these diagnoses do not have a rigorous definition and are physician dependant and therefore reporting between different units may vary. In support of this is data from the UK Renal Registry showing that units which have over 90% of data completion (as comparable with our data set), give an incidence of renovascular disease of 8% and unknown aetiology of 25.5%.

Table 4.5. Referral Data (time = 0)

	Frequency (%)	Mean (95% CI)	Missing data (%)	*Data from ARMS*[δ]
Creatinine at referral (μmol/l)		**515.7** *(488.0-543.3)*	21.4	
Source of referral			18.6	
GP	**25.3**			
A&E	**3.9**			
Hospital transfer	**37.2**			
Diabetic clinic	**3.3**			
Hospital consultant	**30.3**			
Mode of presentation			1.9	
Planned chronic renal failure	**43.8**			***42.7***
Unplanned chronic renal failure	**20.4**			***24.2***
Acute renal failure	**1.1**			***10.7***
Acute on chronic renal failure	**4.8**			***11.8***
End stage renal failure	**18.9**			***10.5***
Lost to follow up	**0.9**			-
Failed transplant	**10.1**			-

[δ]***Metcalfe et al 2000***

Table 4.5 shows that of the SIRS population, 68.9% of patients were seen by renal services at least one month prior to starting dialysis. They were further divided into a planned chronic renal failure group, where appropriate dialysis access was created prior to starting RRT and those without access, the unplanned group, compromising 43.8% and 20.4% of the cohort, respectively. 10% of patients were failed transplants. 20.0% of the cohort presented to renal services less than a month prior to requiring RRT, of these the largest group are patients who present with end stage renal failure (18.9%).

Table 4.6. Dialysis modality and access (time = 0)

	Frequency (%)	Missing data (%)	*Data from UK Renal Registry*
Mode RRT (first session)		0	
CAPD	**34.3**		
HD	**57.6**		***68.2***
Transplant	**1.3**		
Intermittent PD	**3.1**		
APD	**3.1**		
Acute PD	**0.6**		
Access (first session)		1.5	
Tenckhoff	**41.4**		
Temporary internal jugular line	**11.4**		
Temporary subclavian line	**0.8**		
Temporary femoral line	**20.9**		
Semi-permanent internal jugular line	**11.8**		
Semi-permanent subclavian line	**0.2**		
AV fistula - radial	**2.4**		
AV fistula - brachial	**10.0**		
Graft	**0.5**		
PD catheter (rigid)	**0.6**		
Mode RRT (as outpatient)		1.9	
CAPD	**45.0**		
HD	**46.0**		
Transplant	**0.8**		
Intermittent PD	**3.6**		
APD	**4.6**		
Access (as oupatient)		4.5	
Tenckhoff	**54.5**		
Temporary internal jugular line	**5.8**		
Temporary subclavian line	**0.1**		
Temporary femoral line	**1.8**		
Semi-permanent internal jugular line	**21.0**		
Semi-permanent subclavian line	**0.3**		
AV fistula - radial	**3.2**		
AV fistula - brachial	**12.8**		
Graft	**0.5**		
RRT at day 90			
Peritoneal dialysis	**58.0**	0	***28.5***
Haemodialysis	**42.0**		***68.8***
Transplant	**-**		***2.7***

Table 4.6 shows very different practice regarding RRT in the SIRS population compared with the rest of the UK and further investigation of the associations and outcomes of dialysis modality are shown chapter 9. The pre-emptive transplantation rates are low in the

SIRS population, but as this is a reflection of predialysis care, further causes can not be investigated by our study design.

16.5% of our cohort were having haemodialysis using a fistula or graft when they attended for first outpatient dialysis, the commonest being a brachial arterio-venous fistula (12.8%). 29% were using a dialysis line, most common being a semi-permanent internal jugular line (21%), but 7.7% of the cohort were still using temporary access as an outpatient. The influence of access on outcomes is also studied in more detail in chapter 9.

Table 4.7. Centre where RRT commenced (time = 0)

	Frequency (%)	Missing data (%)
Centre		0
Manchester Royal Infirmary	**33.9**	
Hope	**22.4**	
Preston	**33.4**	
Withington	**4.9**	
Satellite	**5.4**	

Table 4.7 shows that most patients start RRT in the main renal centres, which have permanent on-site renal services. Withington hospital renal services closed during the study, which reflects the low acceptance rates. Hope shares it catchment population with a unique satellite unit (in Rochdale) with a stand alone nephrologist. Rochdale is unlike other satellite units, where patients do not start RRT, but it not a main renal centre either (as it does not accept referrals from other hospitals). Given this, a separate category for satellite units (where RRT is commenced was created).

Table 4.8. Co-morbid illnesses (time = 0)

	Frequency (%)	Missing data (%)	*Data from UK Renal Registry*
Diabetes	*25.4*		*21.4*
Non-diabetic patients	74.6		
Type 1	12.7		
Type 2	6.7		
Unspecified	6.0		
CCF	*6.5*	0.9	
Nil	93.5		
NYHA Grade 1	2.7		
NYHA Grade 2	0.6		
NYHA Grade 3	0.7		
NYHA Grade 4	2.5		
Myocardial infarction	*8.8*		
MI <3 months	1.5	1	*3.4*
MI >3 months	7.3	1	*11.0*
Angina	*8.7*	0.9	
Nil	91.3		
NYHA Grade 1	3.8		
NYHA Grade 2	1.3		
NYHA Grade 3	2.3		
NYHA Grade 4	1.3		
CABG/Angioplasty	5.7	1	*4.7*
Peripheral Vascular	*9.2*	0.9	*12.3*
Nil	90.8		
SVS Grade 1	0.7		
SVS Grade 2	3.4		*19.2*
SVS Grade 3	3.1		
SVS Grade 4	2.0		
Ischaemic ulcers	2.5	1	*4.0*
Amputation	2.6	0.9	*1.8*
Non-coronary angioplasty	0.7	0.9	*2.6*
Cerebrovascular disease	6.8	1	*9.7*
Hemiplegia	2.4	0.9	*12.1*
Dementia	0.4	0.9	
COPD	9.5	0.8	*8.6*
Congenital abnormalities	1.7	0.9	
Connective tissue	2.9	0.9	
Liver disease (non-viral)	1.6	0.9	*2.0*
Viral hepatitis	3.5	27.8	
Peptic ulcer disease	1.6	1	
HIV	4.8	64.9	
Leukaemia	0.8	0.9	
Lymphoma	0.4	0.8	
Solid tumour	5.2	0.9	*11.3*
No co-morbidity	43.5		

Table 4.8 shows the high burden of co-morbid illnesses prevalent in the dialysis population. There is less vascular disease in the SIRS population compared with the rest of the UK, suggesting a bias on take-on rates in patients with cardiovascular co-morbidity. However, there is likely to be differences in data recording and methods of data collection and physician reporting of co-morbid illnesses, which may also have resulted in this apparent discrepancy.

Table 4.9. Anthropometric and laboratory data at initiation of RRT (time = 0)

	Median (IQR)	Missing data (%)
Serum sodium (mmol/l)	137 (6)	1.3
Serum potassium (mmol/l)	4.75 (1.2)	1.4
Serum creatinine (μmol/l)	802 (417.5)	1.4
Serum urea (mmol/l)	38.4 (18.9)	1.7
Serum bicarbonate (mmol/l)	21 (7)	16.4
Serum calcium (mmol/l)	2.28 (0.37)	4.4
Serum phosphate (mmol/l)	2.17 (1.05)	5.4
PTH (pg/ml)	263 (353)	43.2
Serum albumin (g/l)	35 (9)	4.9
Haemoglobin (g/l)	94 (27.8)	3
Serum ferritin (μg/l)	179 (221)	29
Serum iron (μg/dl)	10 (7.25)	68.7
Total iron binding capacity (μg/dl)	42 (14)	70
Fe saturation (%)	23 (18)	70
Cholesterol (mmol/l)	4.3 (1.73)	40
Weight (kg)	69.5 (21.5)	22.6
Systolic BP (mmHg)	144 (30)	11.7
Diastolic BP (mmHg)	80 (22)	11.6

Table 4.10. Medical treatment at initiation of RRT (time = 0)

	Frequency (%)	Median (IQR)	Missing data (%)
EPO	37.8		1.5
EPO dose (units)		0 (4000)	2.5
Parenteral iron	12.9		1.6
Oral Iron	25.3		1.6
Statin	31.1		1.7
Antihypertensives			1.8
0	19.7		
1	32.9		
2	30.7		
3	13.2		
4	3.2		
5	0.3		

It is thought that the quality of chronic kidney disease care (predialysis), will affect both the incidence of ESRD and the burden of co-morbid illnesses, and consequently guidelines for the referral and treatment of patients with CKD have been written *(Renal Association 2003)*. With reference to these (as shown in tables 4.9 and 4.10 above), the SIRS population start dialysis with average serum haemoglobin, serum ferritin, serum phosphate, serum PTH and systolic blood pressure outside the recommended standards. The average diastolic blood pressure is at the recommended level for non-diabetic patients, suggesting more than 50% of patients start dialysis with higher than recommended blood pressure, despite the fact that 80.3% are on anti-hypertensive medication. Less than 40% of patients are on EPO and iron therapy. This suggests that the SIRS population start RRT without optimal therapy for CKD, which may contribute to their outcomes.

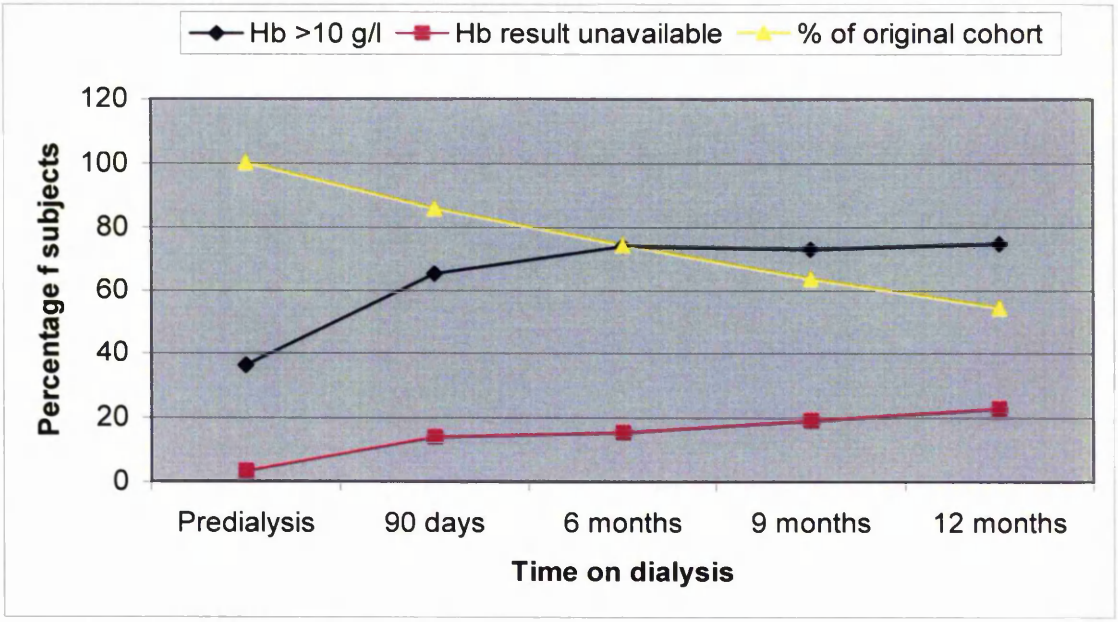
Chapter 5: Implementation of Renal Association standards in patients with End Stage Renal Disease

To produce the results presented in this chapter, data collected at 3 monthly time intervals during the subjects first year of dialysis was analysed (data collection as described in chapter 3). The Renal Association standards referred to in the chapter were published in the 2002 version, 3rd edition, of the standards document.

5.1. Attainment of Renal Association Standards

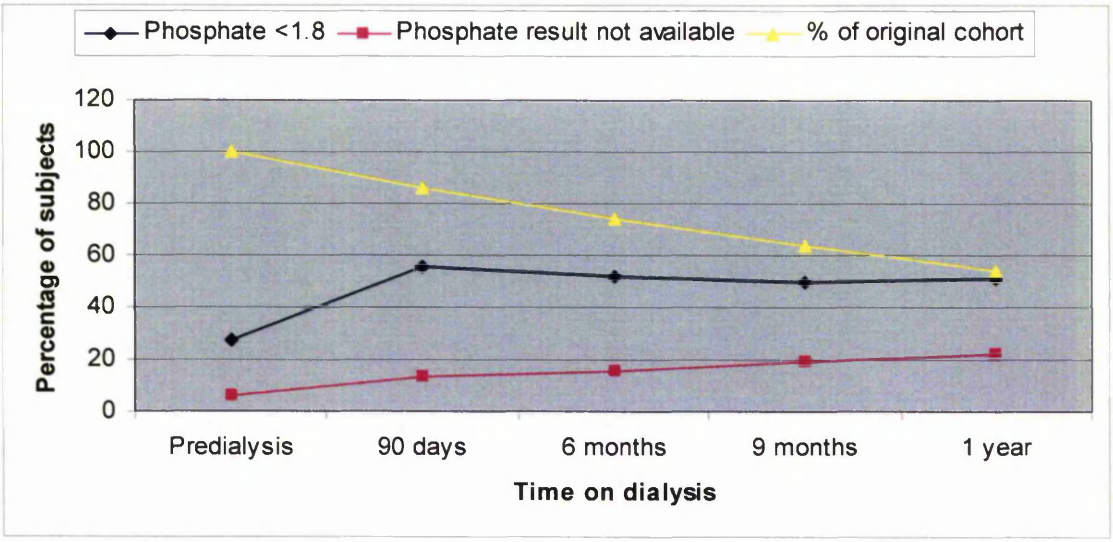
Graphs showing the attainment of the individual standards (excluding missing data) at different time points are shown below. These graphs show the percentage of the original cohort followed up at different time points. A flow chart is presented in chapter 4 to show how and why subjects were not followed up at each time point (figure 4.1). There was a time limit set prior to data collection to say which data were valid for entry onto the study. This was 4 weeks before or after the follow up date for each individual patient. Data outside this time limit, as well as data not measured, was recorded as unavailable in the following graphs and tables.

Graph 5.1. Percentage achievement of Renal Association standard for haemoglobin (Hb) against time on dialysis.



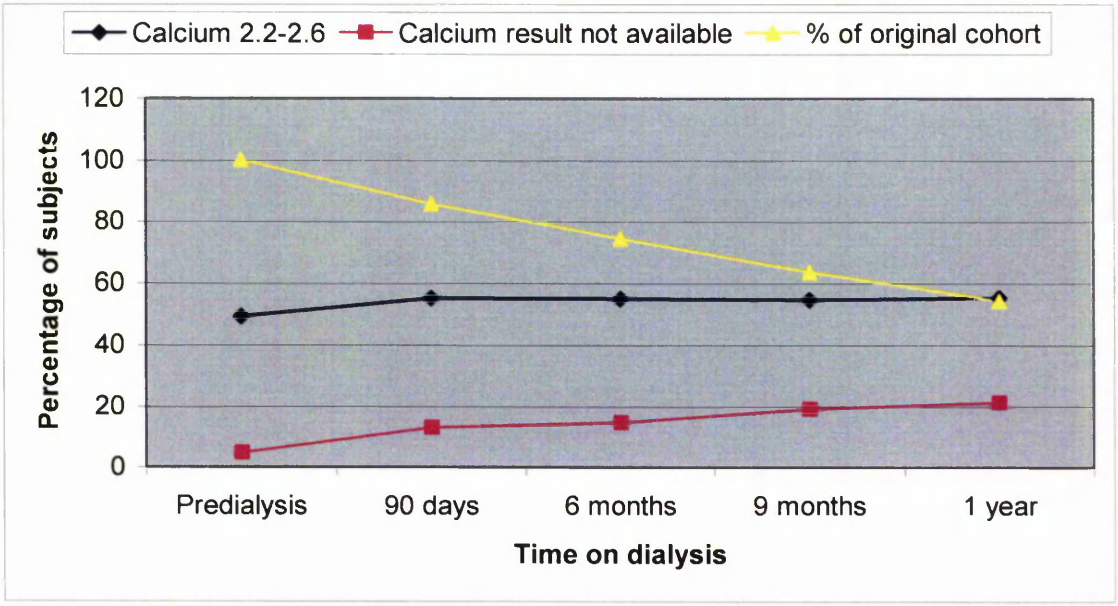
Graph 5.1 shows significant improvement in standard attainment up to 6 months, after which there is little change. Renal anaemia is treated with iron supplements (usually parenteral), erythropoietin and blood transfusions. Physicians try to avoid repeated blood transfusions as this can cause sensitisation making future renal transplantation more difficult. Approximately 20% haemoglobin measurements were unavailable. 75% of patients on dialysis achieved the haemoglobin standard at 1 year.

Graph 5.2. Percentage achievement of Renal Association standard for phosphate (PO) against time on dialysis.



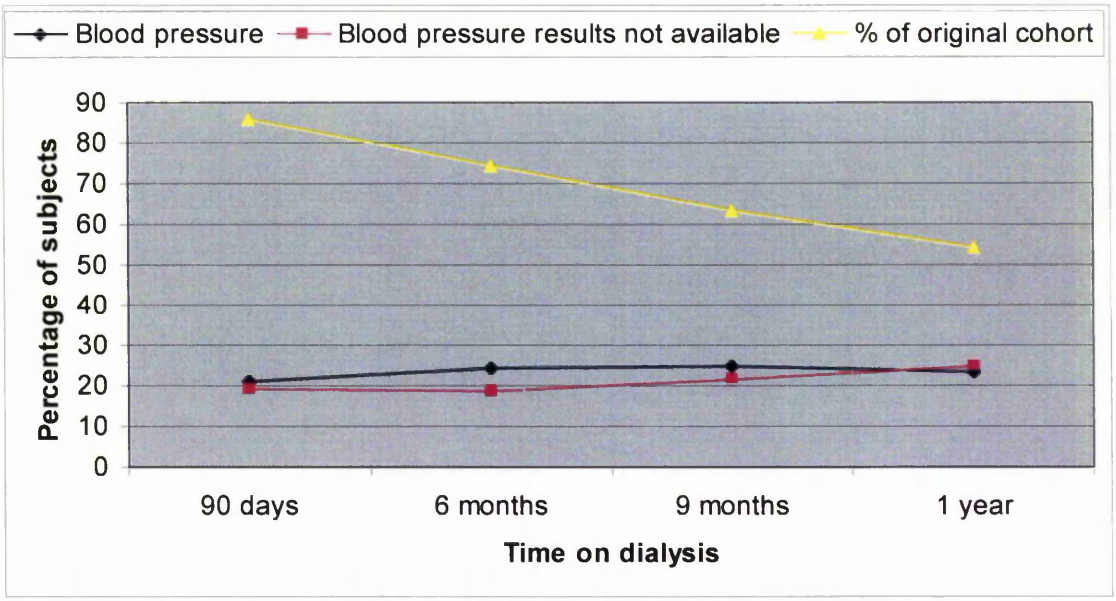
Graph 5.2 shows significant improvement in standard attainment up to 3 months, after which there is little change. This reflects the improvement seen in serum phosphate levels by removal by dialysis, but also the relative inefficiency of the current dialysis regimens in controlling phosphate. Other measures to control phosphate levels are dietary manipulation and phosphate binders. As phosphate is present in many foods and binders are difficult to comply with (patients complain they spoil the taste of a meal) and this is reflected in the low level of standard attainment. Approximately 20% phosphate measurements were unavailable. 51% of patients on dialysis achieved the phosphate standard at 1 year.

Graph 5.3. Percentage achievement of Renal Association standard for calcium (Ca) against time on dialysis.



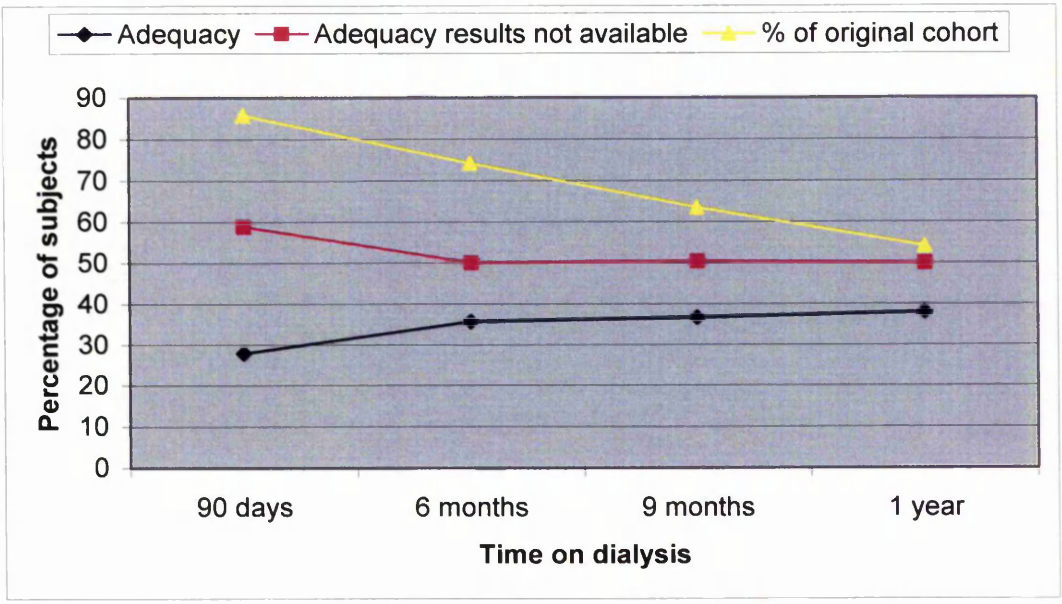
Graph 5.3 shows some improvement in standard attainment up to 3 months, after which there is little change. Calcium levels are dependent on parathormone levels and treatment with 1-alphacalcidol for renal osteodystrophy and on calcium containing phosphate binders (although non-calcium containing binders are available). Approximately 20% calcium measurements were unavailable. 55% of patients on dialysis achieved the calcium standard at 1 year.

Graph 5.4. Percentage achievement of Renal Association standard for blood pressure (BP) against time on dialysis.



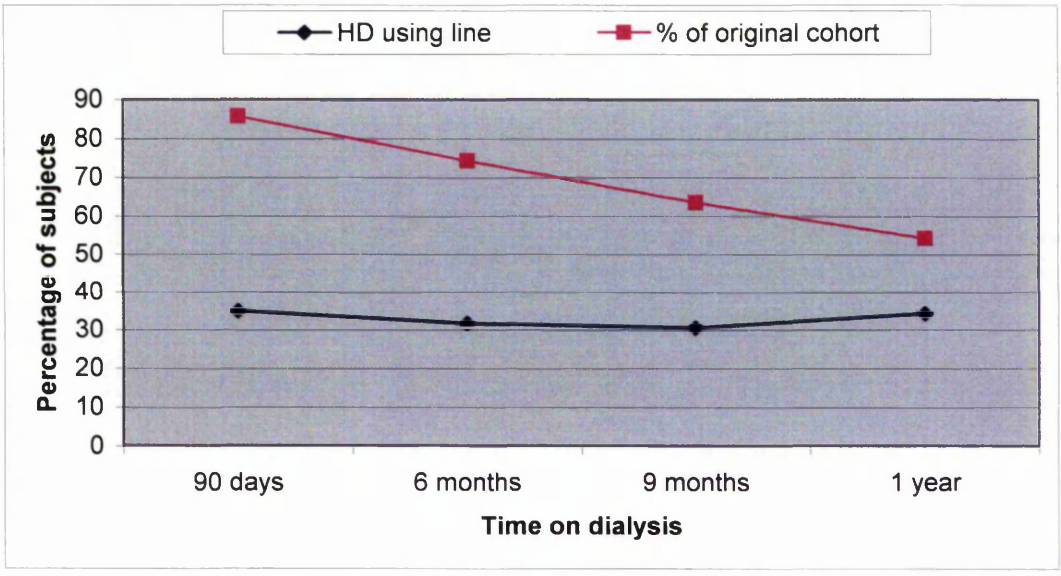
As the blood pressure standard is different depending on dialysis modality and post dialysis blood pressure is also part of the definition, the first time point when this data were collected is at 90 days. Graph 5.4 shows some improvement in standard attainment up to 6 months, after which there is little change. There is a low rate of standard attainment, but partly this is explained by much tighter targets being set by the Renal Association in 2002. Prior to this most units worked to a standard of less than 140/90 mmHg for patients less than 65 years and less than 160/90 mmHg for patients over 65 years. There is known to be a delay between standards being published and becoming practice in renal units *(Renal Association 2002)*. Blood pressure is treated by fluid removal on dialysis and by antihypertensive medications. Approximately 20% of blood pressure measurements were unavailable. 23% of patients on dialysis achieved the blood pressure standard at 1 year.

Graph 5.5. Percentage achievement of Renal Association standard for dialysis adequacy for haemodialysis and peritoneal dialysis, against time on dialysis.



The first time point when adequacy data were collected is at 90 days. The curve shows some improvement in standard attainment up to 6 months, after which there is a gradual but continuing improvement in standard achievement. This may be because as the time on dialysis becomes longer, patients prescriptions are changed, or dialysis modality is changed or patients with low adequacy standards are removed from the study (by death or transplantation). The most likely cause, however, is the high rate of unavailability of measures of dialysis adequacy (60%). 38% of patients on dialysis achieved the adequacy standard at 1 year.

Graph 5.6. Percentage of patients using a dialysis catheter for haemodialysis against time on dialysis.



Only patients who started and continued on haemodialysis were included in the above graph. If they switched between dialysis modality or were transplanted in their first year on RRT, they were excluded from this analysis. This is owing to the difficulty in saying how long they had been on haemodialysis, which is likely to affect access provision. There is no significant change in the proportion of haemodialysis patients using a dialysis line over 1 year (approximately 33%). There was less than 1% of data unavailable/missing at any time point. This suggests that in some patients it is very difficult to create fistula access, and is not simply lack of resources. Fistula patency and functionality were not recorded as part of the study.

Graphs 5.1 to 5.7 show that there is a significant attrition rate of study subjects. The numbers in each time cohort and reasons for not being available for follow up are shown in detail in figure 4.1 (chapter 4). At 6 months, 820 subjects (74%) were followed up. Therefore it was this time point used to assess standard attainment in the following analyses. It is noted that the cohort characteristics will be different at 3 months and 12 months, which may effect the associations with standard attainment, but 3 months was felt to be too short a period of time for standard attainment and the study was not long enough to have sufficient numbers for analysis at 12 months. Mode of dialysis (HD or PD) was recoded as a separate variable. Each analysis was adjusted for mode of dialysis. More detailed study of the impact of dialysis modality and access in discussed in chapter 9.

5.2. Predictors of achievement of Renal Association standards

Following on from this logistic regression analysis was performed to uncover the independent predictors of achievement of the individual standards at 6 months.

5.2.1. "Missing" Data

Individual patient data were recorded if it fell 4 weeks either side of the follow up date, therefore "missing" data reflects either non-recording of the variable or recording of the variable outside the time limit. Of course, it is not known whether the data which is not recorded would have represented achievement or non-achievement of the standards, therefore 2 separate analyses were done, 1 recording the "missing" data as failure to achieve the standard and the other removes all missing data from the analysis. In this manner any bias in recording the data will also be highlighted.

5.2.2. Logistic Regression

Most of the graphs above show little change after 6 months, therefore achievement of the standards at 6 months was used to represent the desired outcome. The factors in the logistic regression were age, gender, ethnicity (white and non-white), Townsend score (a marker for social deprivation), renal diagnosis (glomerulonephritis, interstitial nephritis, diabetic nephropathy, renovascular disease, other multi-system disorders and unknown aetiology), mode of presentation (planned CRF, unplanned CRF, late referral and failed transplants), vascular co-morbidity (including CCF, angina, previous myocardial infarctions, CABG/angioplasty, peripheral vascular disease and cerebrovascular disease), GFR at initiation of dialysis (calculated using the Cockcroft and Gault formula), serum albumin, mode of dialysis (haemodialysis using a fistula or graft, haemodialysis using a dialysis catheter and peritoneal dialysis) and centre (Satellite, Hope, MRI, Preston and Withington).

Table 5.1. Predictors of Achievement of Haemoglobin Standard at 6 months

	Unavailable haemoglobin results recorded as failing to achieve standard AOR$^{\delta}$ (95% CI)	Unavailable haemoglobin results recorded as missing AOR$^{\delta}$ (95% CI)
Age	**1.03 (1.01-1.05)** *p<0.001*	**1.03 (1.02-1.05)** *p<0.001*
Serum albumin	**1.11 (1.06-1.17)** *p<0.001*	**1.13 (1.08-1.18)** *p<0.001*
Peritoneal dialysis *(reference category = HD with fistula)*	**1.89 (1.01-3.55)** *p=0.047*	**2.31 (1.19-4.49)** *p=0.013*
Haemodialysis with line *(reference category = HD with fistula)*	**0.43 (0.22-0.86)** *p=0.017*	**0.43 (0.21-0.87)** *p=0.019*

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre***

Older patients are more likely to achieve a haemoglobin >10 g/dl. The most likely reason is that younger patients are less symptomatic with low haemoglobin levels and therefore, are less likely to receive blood transfusions. However, to avoid long term damage to cardiac muscle this group should be treated more aggressively. Low serum albumin is associated with a failure to achieve the haemoglobin standard. This may reflect ill health and a degree of inflammation. Low haemoglobin is associated with a pathological inflammatory response, partly because in such a state the bone marrow is less response to erythropoietin (endogenous and exogenous). Patients on peritoneal dialysis are more likely, and patients on HD using a line less likely to achieve the haemoglobin standard. The most likely explanation is because patients on haemodialysis tend to lose some blood each time they have a dialysis session.

Table 5.2. Predictors of Achievement of Phosphate Standard at 6 months

	Unavailable phosphate results recorded as failing to achieve standard AOR$^{\delta}$ (95% CI)	Unavailable phosphate results recorded as missing AOR$^{\delta}$ (95% CI)
Age	**1.03 (1.02-1.05)** ***p<0.001***	**1.03 (1.02-1.05)** ***p<0.001***
Diabetic nephropathy ***(reference category = glomerulonephritis)***	**2.27 (1.13-4.54)** ***p=0.02***	**2.11 (1.05-4.25)** ***p=0.037***
Withington ***(reference category = Satellite unit)***	**0.33 (0.11-0.98)** ***p=0.047***	**0.27 (0.09-0.85)** ***p=0.024***

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre***

Older patients are more likely to achieve the standard for phosphate control. Patients with diabetic nephropathy are more likely to achieve the standard compared with patients with other renal diagnoses. Both these factors are likely to reflect reduced intake of dietary phosphate, but without formal assessment of diet this remains a hypothesis. Patients dialysing at Withington were less likely to achieve the standard than other units.

Table 5.3. Predictors of Achievement of Calcium Standard at 6 months

	Unavailable calcium results recorded as failing to achieve standard AOR$^{\delta}$ (95% CI)	Unavailable calcium results recorded as missing AOR$^{\delta}$ (95% CI)
GFR at initiation of dialysis	**1.10 (1.03-1.18)** ***p=0.003***	**1.10 (1.03-1.18)** ***p=0.003***

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre***

As shown in table 5.3, a lower GFR at initiation of dialysis is associated with failure to achieve the calcium standard.

Table 5.4. Predictors of Achievement of Blood Pressure Standard at 6 months

	Unavailable blood pressure results recorded as failing to achieve standard AOR$^{\delta}$ (95% CI)	Unavailable blood pressure results recorded as missing AOR$^{\delta}$ (95% CI)
Albumin	**0.94 (0.90-0.98)** *p=0.007*	**0.99 (0.90-0.99)** *p=0.02*
Interstitial Nephritis ***(reference category = glomerulonephritis)***	**1.95 (1.01-3.81)** *p=0.048*	**2.06 (1.04-4.06)** *p=0.038*
Hope ***(reference category = Satellite unit)***	**3.31 (1.01-10.78)** *p=0.048*	**Not statistically significant**

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre***

Low serum albumin is associated with achieving the blood pressure standard (i.e. low blood pressure). Patients with a primary renal diagnosis of interstitial nephropathy are more likely to achieve the blood pressure standard than patients with other renal diagnoses. The results above suggest that it was more difficult to record blood pressure measurement on to the study from the renal unit at Hope, but of those measured there was no difference in standard achievement. Other factors may be important, but may not have shown up in the analysis given the low level of standard attainment.

Table 5.5. Predictors of Achievement of Adequacy Standard at 6 months

Factor	Unavailable adequacy results recorded as failing to achieve standard AOR$^{\delta}$ (95% CI)	Unavailable adequacy results recorded as missing AOR$^{\delta}$ (95% CI)
Female gender	1.57 (1.05-2.35) *p=0.029*	4.83 (2.18-10.7) *p<0.001*
White (ethnic group)	Not statistically significant	0.24 (0.08-0.68) *p=0.007*
GFR at initiation of dialysis	Not statistically significant	0.89 (0.80-0.99) *p=0.039*
Diabetic nephropathy *(reference category = glomerulonephritis)*	0.50 (0.25-0.99) *p=0.046*	Not statistically significant
Late referral *(reference category = Planned CRF)*	Not statistically significant	0.32 (0.13-0.74) *p=0.008*
Peritoneal dialysis *(reference category = HD with fistula)*	Not statistically significant	7.72 (3.06-19.48) *p<0.001*
Withington *(reference category = Satellite unit)*	0.33 (0.11-0.96) *p=0.041*	Not statistically significant
MRI *(reference category = Satellite unit)*	0.30 (0.13-0.71) *p=0.006*	Not statistically significant

$^{\delta}$*Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre*

Table 5.5. shows that females are more likely to achieve the adequacy standard. This is likely to be because of their relatively lower body surface area compared with men, making dialysis more effective. However, it may also reflect a false positive result as creatinine and urea are lower in people with less muscle mass. The other associations probably reflect factors associated with failure to measure or record dialysis adequacy. Recording adequacy measurements is more difficult in diabetic patients (hypotheses include the high hospitalisation rates seen in these patients and adequacy measures are routinely done on an outpatient basis); patients from ethnic minorities (maybe because of language difficulties causing incomplete compliance with testing); patients referred late (these patients are in hospital for longer initially); patients on peritoneal dialysis (testing for adequacy of peritoneal dialysis is more complicated than testing for adequacy of haemodialysis and requires considerable staff and patient input) and patients dialysing at MRI and Withington.

Table 5.6. Predictors of Achievement of Access Standard at 6 months

	AOR[δ] (95% CI) for Access standard
Age	**0.98 (0.96-0.99)**
	p=0.013
Female gender	**0.60 (0.37-0.99)**
	p=0.05
Townsend Score	**0.93 (0.87-0.99)**
	p=0.029
Serum albumin	**0.95 (0.90-0.99)**
	p=0.049
Failed transplant	**0.31 (0.13-0.72)**
(reference category = planned CRF)	***p=0.006***
Late referral	**0.14 (0.07-0.26)**
(reference category =planned CRF)	***p<0.001***

[δ]Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin and centre

As seen from table 4.6, missing data were less than 1%, therefore only one analysis is undertaken to look for independent predictors of the access standard. Older patients and female patients are less likely to achieve the access standard, this is likely to reflect the increased technical difficulty in creating fistulas in these groups. Patients who are more socially deprived are less likely to achieve this standard. This has not been noted before and one possible hypothesis is that this may reflect poor compliance, in terms of attendance for pre-procedure work-up clinics. Patients with a low serum albumin are less likely to achieve this standard. Albumin often reflects the overall health of a patient and nephrologists will avoid creating permanent access in patients who are unwell as there are higher rates of failure and complications (but this may also reflect that those with lines have a lower serum albumin, possibly secondary to ongoing infections). Patients who are referred late are less likely to achieve this standard within 1 year of starting dialysis. Failed transplants are less

likely to achieve this standard during their subsequent dialysis career than patients who have been referred early and have not had dialysis previously (planned CRF group). Again this may reflect increased difficulty in creating permanent access in patients who have dialysed previously and had previous access made.

5.3. Outcomes of Non-achievement of Renal Association standards

5.3.1. Individual standards

The outcomes (mortality, transplantation and hospitalisation) are shown for the individual standards. A Cox Regression analysis was carried out. The odds ratio reflects the association between failure to achieve the Renal Association standard at 6 months and the selected outcome. The 6 month time point was selected from the above graphs, because the curves were flat at this point (reflecting little change in standard attainment after this point and 70% of the original cohort were still on the study). Separate analyses were done for data that was not available. Hospitalisation was recorded after 6 months on the study, as this was the time point when achievement of the standard was assessed. This was not necessary for mortality and transplantation, as these patients are withdrawn from the study at this point.

Table 5.7(a). Adjusted odds ratios (AOR) for outcome of non-achievement of Renal Association standards at 6 months (unavailable data coded as failure to achieve standard)

Standards	AOR$^{\delta}$ (95% CI) Hospitalisation	AOR$^{\delta}$ (95% CI) Mortality	AOR$^{\delta}$ (95% CI) Transplantation
Haemoglobin	1.22 *(0.80-1.86)*	1.01 *(0.61-1.66)*	0.53 *(0.26-1.09)*
Phosphate	1.80** *(1.25-2.60)*	1.69** *(1.05-2.66)*	0.82 *(0.43-1.55)*
Calcium	1.16 *(0.80-1.69)*	0.67 *(0.42-1.07)*	1.03 *(0.56-1.86)*
Blood pressure	0.58** *(0.39-0.85)*	0.82 *(0.51-1.31)*	1.96 *(0.94-4.09)*
Dialysis Adequacy	1.70** *(1.16-2.47)*	1.61* *(1.01-2.57)*	1.21 *(0.66-2.19)*
Access	1.50 *(0.97-2.32)*	1.91* *(1.17-3.18)*	0.34 *(0.10-1.16)*

$^{\delta}$*Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre*

**p<0.05 **p<0.005*

Table 5.7(b). Adjusted odds ratios (AOR) for outcome of non-achievement of Renal Association standards at 6 months (unavailable data coded as missing)

Standards	AOR$^{\delta}$ (95% CI) Hospitalisation	AOR$^{\delta}$ (95% CI) Mortality	AOR$^{\delta}$ (95% CI) Transplantation
Haemoglobin	1.29 *(0.82-2.05)*	1.02 *(0.60-1.70)*	0.53 *(0.24-1.19)*
Phosphate	1.79** *(1.24-2.59)*	1.68** *(1.06-0.68)*	0.88 *(0.46-1.67)*
Calcium	1.17 *(0.81-1.71)*	0.65 *(0.40-1.04)*	1.05 *(0 .58-1.90)*
Blood pressure	0.57** *(0.38-0.84)*	0.80 *(0.50-1.29)*	1.94 *(0.92-4.08)*
Dialysis Adequacy	1.98 *(0.97-4.01)*	1.01 *(0.46-2.23)*	6.45** *(1.83-22.6)*
Access	1.50 *(0.97-2.32)*	1.91* *(1.17-3.18)*	0.34 *(0.1-1.16)*

$^{\delta}$*Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre*

**p<0.05; **p<0.005*

Failure to achieve the phosphate standard is associated with greater odds of mortality and hospitalisation. Failure to achieve the access standard is associated with mortality. Failure to measure the adequacy standard is more likely in patients at greater risk of mortality, hospitalisation and failing to be transplanted.

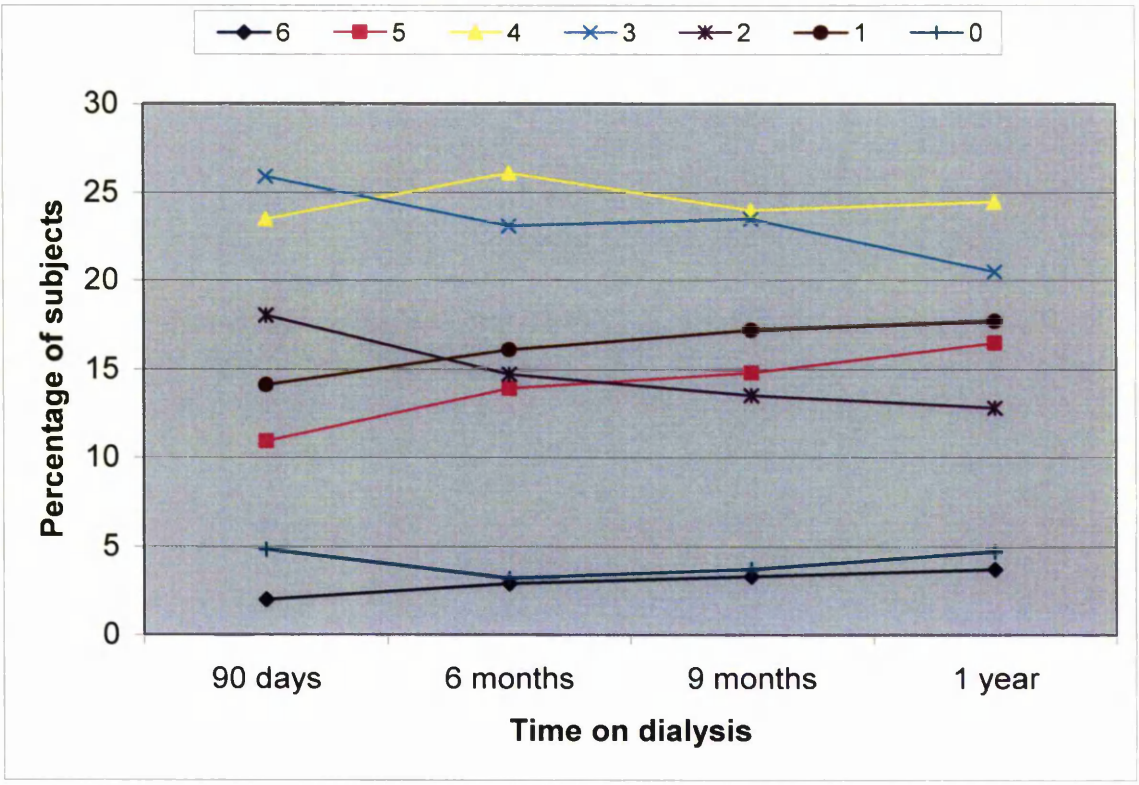
The only other study looking at the impact of Renal Association standards on mortality found that achieving the standard for haemoglobin and albumin, but not haemodialysis adequacy, was associated with better survival in patients with ESRD. The authors used mean levels over an 18 month follow up period, and found a mean haemoglobin level of >10 g/dl in 69% of a total cohort of 396 *(Metcalfe et al 2003)*. Our analysis found a strong association between low haemoglobin and low albumin. Therefore in our model, which did not use serum albumin as an individual standard, but instead a confounding factor reflecting a "sick" patient, haemoglobin was not independently associated with mortality.

5.3.2. Collective standards

Each standard that was achieved was scored 1 and non-achievement of standards was scored as 0. From this a score was calculated for all the standards, with 6 reflecting achievement of all standards at a given time and 0 reflecting the non-achievement of all standards. As the number of patients scoring 6, i.e. achieving all standards, was so small, scores of 5 and 6 were combined so logistic regression and Cox regression analysis could be performed.

The number of individual standards achieved by each subject is shown in graph 5.7.

Graph 5.7. Percentage of subjects achieving Renal Association standards against time on dialysis



Graph 5.7 shows that overall there is an improvement towards more standards being achieved after 1 year on dialysis, with a greater percentage of patients achieving 4 or more standards after 1 year (35.5% versus 45%). Subjects achieving all and those achieving none of the standards are in the smallest groups.

Table 5.8. Unadjusted and adjusted odds ratios (OR) for mortality for the number of individual standards achieved, using time dependant Cox regression over 1 year

Number of standards achieved	Unadjusted OR *(95% CI)*	Adjusted OR[δ] *(95% CI)*
6 + 5	1.00 *(reference)*	1.00 *(reference)*
4	0.73 *(0.45-1.19)*	0.73 *(0.41-1.29)*
3	1.00 *(0.63-1.59)*	0.89 *(0.5-1.59)*
2	1.02 *(0.61-1.69)*	1.32 *(0.73-2.39)*
1	1.70* *(1.04-2.76)*	1.58 *(0.85-2.9)*
0	3.64** *(2.02-6.57)*	2.11 *(0.98-4.56)*

[δ]***Adjusted for age, gender, ethnicity, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity, GFR at initiation of dialysis, serum albumin, mode of dialysis and centre***

****p<0.05***

*****p<0.005***

Time dependant Cox regression analysis selects the nearest data entry point prior to the event. The intention of this analysis was to see whether the Renal Association standards as a whole could be used to predict mortality. The achievement of standards overall reflected a better unadjusted survival, but only showed a trend when adjustments were made for other factors including vascular disease and diabetic nephropathy. This would suggest that achieving the standards is associated with better outcome, but a significant proportion of patients start dialysis with other factors, e.g. vascular co-morbidity, which give them a poor outcome regardless of the standards they achieve. It is to be noted, however, that mortality is not the only outcome of care for patients with ESRD. Further work needs to be done to assess whether these standards improve morbidity and quality of life.

Chapter 6: Influence of Ethnic group in patients with End Stage Renal Disease

Data on ethnic origin is available for 97.7% of the SIRS cohort. The ethnic groups recorded are consistent with the UK Renal Registry and consist of Indo-Asians (9.4%), Black (3%) and Chinese (0.5%).

6.1. Take-on rates for RRT in Ethnic minority groups

Data from UK census 2001 estimates the population of the Northwest at 6.03 million and ethnic minority populations as Indo-Asian + including mixed race of 2.59% + 2.88%; Black +mixed race of 0.7% + 1.22% and Chinese + mixed race of 0.8% + 1.02%. The SIRS catchment population is only 4.5 million in comparison, but data from 1991 census which looks at ethnic minorities in different local authority areas suggests the area in the Northwest not covered by SIRS has less ethnic minority groups. Therefore the proportions of the different ethnic minority groups were recalculated assuming a total population of 4.5 million. This gives the ethnic minority populations as Indo-Asian + including mixed race of 3.91% + 4.35%; Black +mixed race of 1.05% + 1.80% and Chinese + mixed race of 1.2% + 1.55%. This assumption gives the maximum number of people from ethnic minority groups. Despite this it can be seen that the Indo-Asian and Black population are over-represented in the ESRD population (2-3 times), but not the Chinese population. Due to the error in calculating the overall general population, the exact increase cannot be stated with certainty.

6.2. Characteristics of different Ethnic groups with ESRD

Table 6.1 shows the unadjusted characteristics of each ethnic group. It is difficult to draw any conclusions about the characteristics of the Chinese population given that there are only 5 subjects from this ethnic group on the study. Similarly, differences in the Black population alone are unlikely to reach statistical significance given the small number of subjects. Some inferences can be drawn about these groups, but with caution.

Table 6.1 Unadjusted associations with ethnicity

	White (n=945)	Indo-Asian (n=102)	Black (n=32)	Chinese (n=5)	p-value[α]
Mean Age *(years)* (95% CI)	57.8 (56.8-58.9)	53.7 (50.8-56.5)	56.1 (50-62.2)	66.7 (56-77.4)	0.05[β]
Sex					>0.05
Male	61.7	56.9	46.9	60	
Female	38.3	43.1	53.1	40	
Social Deprivation					<0.001
Townsend Quintile:					
1st	12.4	1.2	6.9	20	
2nd	9.3	1.2	0	20	
3rd	16.3	6.2	13.8	20	
4th	23.4	6.2	10.3	0	
5th	38.7	85.2	69	40	
Marital Status					0.008
Married	63.4	81.8	48.3	100	
Single	21	8.0	27.6	0	
Divorced/separated	6.2	3.4	10.3	0	
Widowed	9.4	6.8	13.8	0	
Pack years					<0.001
0	53.7	87.9	85.7	100	
>0	46.3	12.1	14.3	0	
Mode of presentation					>0.05
Planned CRF	45.6	38.8	33.3	40	
Unplanned CRF	21.1	21.4	20	40	
Late referrals	23.3	30.6	33.3	20	
Failed transplants	10	9.2	13.3	0	

[α] *Chi squared test (unless stated otherwise)*

[β] *One way ANOVA*

Table 6.1 continued	White (n=945)	Indo-Asian (n=102)	Black (n=32)	Chinese (n=5)	p-value[α]
Renal diagnosis					0.012
Glomerulonephritis	16.5	9.8	15.6	0	
Interstitial nephritis	22.5	14.7	9.4	0	
Renovascular	7.0	6.9	9.4	0	
Diabetic nephropathy	19.0	27.5	34.4	60	
Other multisystem	11.4	9.8	9.4	20	
Unknown	23.3	31.4	21.9	20	
Diabetes					<0.001
No	76.1	61.8	59.4	40	
Yes	23.9	38.2	40.6	60	
Vascular disease					>0.05
No	69.5	66.7	75	80	
Yes	30.5	33.3	25	20	
Centre					0.02
Satellite	5.1	3.9	6.3	20	
MRI	29.9	36.3	59.4	40	
Hope	25.0	23.5	18.8	0	
Preston	33.8	34.3	15.6	40	
Withington	6.2	2	0	0	

[α] *Chi squared test (unless stated otherwise)*

[β] *One way ANOVA*

Table 6.1 shows that Indo-Asians with ESRD are younger than the white population. The male: female ratio for incidence of ESRD is reversed in the Black population, consistent with results from the UK Renal Registry *(UK Renal Registry. Sixth Annual Report. 2003.)* More Indo-Asian and Black patients, who develop ESRD, belong to the most socially deprived group than White patients. A greater proportion of Indo-Asian patients are married. There were no significant differences in mode of presentation but 33% of Black subjects were likely to present late to renal services compared with 23% of White subjects. White patients are almost three times as likely to have or still be smoking cigarettes. Diabetes and diabetic nephropathy are more prevalent in patients from ethnic minorities, but there was no difference in prevalence of vascular disease in these populations. MRI had a much higher population of Black patients than other centres.

6.3. Comparison between Indo-Asian and White Ethnic groups with ESRD

Table 6.2 shows associations with patients from Indo-Asian ethnic minority groups who develop ESRD compared with White patients. Analysis was not done for Black or Chinese patients because of the small numbers of subjects in these groups, which are likely to create significant errors in the reported results. A logistic regression analysis was performed using Indo-Asian as the outcome. The factors in the logistic regression were age, gender, Townsend score (a marker for social deprivation), marital status (married, single, divorced/separated and widowed), renal diagnosis (glomerulonephritis, interstitial nephritis, diabetic nephropathy, renovascular disease, other multisystem disorders and unknown aetiology), mode of presentation (planned CRF, unplanned CRF, late referral and failed transplants), vascular co-morbidity (including CCF, angina, previous myocardial infarctions, CABG/angioplasty, peripheral vascular disease and cerebrovascular disease) and centre (Satellite, Hope, MRI, Preston and Withington).

Table 6.2 Adjusted odds ratios (OR) for Indo-Asian ethnic minority

Factor	Adjusted[δ] OR	95% CI	p-value
Age	0.95	0.93-0.97	<0.001
Male gender	0.71	0.60-1.93	>0.05
Townsend score	1.28	1.19-1.38	<0.001
Marital Status			
Married	1 (reference)		
Single	0.12	0.14-0.33	<0.001
Separated	0.20	0.04-0.92	0.04
Widowed	0.63	0.21-1.92	>0.05
Primary Renal Diagnosis			
Glomerulonephritis	1 (reference)		
Interstitial nephritis	1.25	0.46-3.39	>0.05
Renovascular disease	2.62	0.72-9.60	>0.05
Diabetic Nephropathy	1.25	0.46-3.43	>0.05
Other Multi-system	1.08	0.32-3.60	>0.05
Unknown	1.72	0.68-4.34	>0.05
Mode of Presentation			
Planned CRF	1 (reference)		
Unplanned CRF	0.88	0.4-1.94	>0.05
Late referrals	1.52	0.77-2.97	>0.05
Failed transplants	0.67	0.25-1.87	>0.05
Vascular disease	1.70	0.90-3.22	>0.05
Centre			
Satellite	1 (reference)		>0.05
MRI	3.02	0.34-26.5	>0.05
Hope	2.03	0.15-26.5	>0.05
Preston	4.60	0.55-38.59	>0.05
Withington	3.24	0.38-27.6	>0.05

[δ]*Adjusted for age, gender, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity and centre*

Table 6.2 shows that patients from Indo-Asian ethnic minority group, who had ESRD, were younger, more socially deprived and more likely to be married. Cigarette smoking was not included in this analysis because more than 15% of this data were missing, and may therefore skew the analysis (the ethnic minority patients may be a more select group, i.e. may not speak and read English and therefore not answer our questions).

The ethnic minority population is growing older and ESRD is more common in older age groups. As yet the population of the Indo-Asian ethnic minority with ESRD requiring RRT is young, but as the general population of Indo-Asians grows older there is likely to be a significant increase in demand for RRT.

There is no evidence from our study that Indo-Asian subjects have more diabetic nephropathy once adjustments are made for age. The logistic regression analysis was re-done excluding diabetic nephropathy and including diabetes, but this did not show increased adjusted rates of diabetes in the Indo-Asian population compared with the White population. Other studies (see chapter 1) have shown an increased incidence of diabetes in the Indo-Asian population. It may be that the association between social deprivation and diabetes (as shown in the next chapter) is stronger than the association between diabetes and Indo-Asian ethnic minority, in our population.

From our study of this population, there is a strong association between social deprivation and the Indo-Asian group. This may be where the answer lies in how to reduce ESRD in ethnic minorities. A detailed analysis of social deprivation and ESRD is provided in the next chapter. However, the Townsend Score (a marker for social deprivation), used by the UK Renal Registry, is not validated in ethnic minorities, and this population should re-analysed when a validated social deprivation score is created.

6.4. Outcomes of Indo-Asian patients compared with White patients with ESRD

Table 6.3 shows the adjusted outcomes (hospitalisation, mortality and transplantation) for Indo-Asian patients with ESRD. The analysis was done using Cox Regression.

Table 6.3 Adjusted odds ratios for outcomes in Indo-Asian patients with ESRD.

	Unadjusted Odds Ratio *(95% CI)*	**Adjusted$^{\delta}$ Odds Ratio** *(95% CI)*
Hospitalisation	1.02 *(0.89-3.02)*	1.18 *(0.80-1.75)*
Mortality	1.39 *(0.89-2.17)*	1.64 *(0.89-3.02)*
Transplantation	1.17 *(0.61-2.25)*	0.88 *(0.42-1.86)*

$^{\delta}$***Adjusted for age, gender, Townsend score, mode of presentation, renal diagnosis, vascular co-morbidity and centre***

This shows that, once receiving dialysis, the outcomes of Indo-Asians were the same as White patients.

Based on the 2001 UK Census data, a Townsend score, a surrogate marker for social deprivation, was allocated for postcodes in England and Wales. The Townsend score is based on the total unemployment, number of no car households, house overcrowding and number of non-owner occupied households in each local authority, using data from the 2001 census. A Townsend score, using patient postcodes, was assigned to each subject in our study. It has been shown to correlate with other measures of social deprivation *(Morris and Carstairs 1991).* It has not been validated in ethnic minorities. Higher scores indicate more social deprivation.

7.1. Comparison of SIRS population with UK Renal Registry

For analysis the group presenting as failed transplants were excluded, so comparison could be made with results from the UK Renal Registry (which excludes this group). Therefore, there were 979 patients available for analysis. Of these, a Townsend score could be calculated on 87% or 851 patients.

Mean Townsend score for the cohort was 1.84 (95% confidence interval of 1.55 to 2.12) and median score was 1.63 (interquartile range 6.08). The UK Renal Registry 2003 found patients accepted for RRT in the UK were more deprived than the general population (0.08; 95% CI 0.03 to 0.14, compared with -0.448). The mean of our study population (1.84; 95% CI 1.61 to 2.11) indicates more social deprivation in the population starting RRT in the North West compared with the rest of the UK.

7.2. Factors associated with social deprivation

Unadjusted analysis (table 7.1) shows that patients from ethnic minorities have a higher social deprivation score. Patients with ESRD who are married are less socially deprived. Patients with diabetes were more likely to be socially deprived, but there was no association between vascular disease, smoking and social deprivation. The UK Renal Registry found no association between cardiovascular disease and social deprivation, but did find a higher incidence of cigarette smoking in socially deprived groups. It is noted that almost 50% of the SIRS data on smoking is missing, and it may be that patients who answered our questionnaires were less socially deprived and therefore skewed the results. Social deprivation was associated with late referral to renal services in our population and, also, starting dialysis without functioning access in those who had been followed up for longer than 1 month (the unplanned renal failure group). The UK Renal Registry notes less social deprivation in patients with ESRD from the South of England compared with the North. Indeed, 2 main units in our study, MRI and Hope had higher mean Townsend scores than renal units in the rest of the UK.

Table 7.1. Unadjusted associations with social deprivation.

	Mean Townsend score[γ] (95% CI)	Missing data (%)	p-value[β]
Total cohort (n=979)	1.84 (range -6.29 to 13.08)	13	
Age		0	>0.05
<65 yrs	2.07 (1.70, 2.44)		
>65 yrs	1.55 (1.12, 1.98)		
Sex		0	>0.05
Male	1.68 (1.32, 2.04)		
Female	2.09 (1.64, 2.53)		
Ethnic minority		2.2	<0.001
White	1.38 (1.09, 1.67)		
Non-white	4.98 (4.16, 5.80)		
Marital Status		9.5	0.002
Married	1.48 (1.12, 1.83)		
Single	2.56 (1.85, 3.26)		
Divorced/separated	3.23 (2.09, 4.38)		
Widowed	2.44 (1.41, 3.47)		
Pack years		48.4	>0.05
0	2.12 (1.59, 2.66)		
>0	1.97 (1.41, 2.53)		
Renal diagnosis		0	>0.05
Glomerulonephritis	1.70 (1.01, 2.40)		
Interstitial nephritis	1.14 (0.59, 1.7)		
Renovascular	1.72 (0.5, 2.95)		
Diabetic nephropathy	2.53 (1.91, 3.16)		
Other multisystem	2.20 (1.34, 3.05)		
Unknown	1.77 (1.19, 2.35)		

Table 7.1 continued	Mean Townsend score[γ] (95% CI)	Missing data (%)	p-value[β]
Diabetes		0	0.003
No	1.58 (1.25, 1.90)		
Yes	2.54 (1.99, 3.08)		
Vascular disease		0.6	>0.05
No	1.78 (1.44, 2.12)		
Yes	1.99 (1.49, 2.50)		
Mode of presentation		0	0.002
Planned CRF	1.34 (0.96, 1.73)		
Unplanned CRF	2.53 (1.93, 3.12)		
Late referral	2.11 (1.56, 2.66)		
Centre		0	<0.001
Satellite	0.40 (-0.94, 1.74)		
MRI	3.09 (2.55, 3.64)		
Hope	2.53 (2.04, 3.02)		
Preston	0.54 (0.1, 0.97)		
Withington	-0.18 (-1.15, 0.79)		

[γ] *Higher scores indicate more social deprivation.*

[β] *One way ANOVA.*

7.3. Independent associations with social deprivation

3 separate analyses were done to find independent associations with social deprivation. These were: a multiple linear regression analysis using Townsend score; a logistic regression, dividing the SIRS population into 2 groups using the median Townsend score and a multinomial logistic regression and dividing the cohort into Townsend quintiles. These analyses did not yield any different results to the unadjusted analysis shown above and are therefore not shown.

Social deprivation in the SIRS population affected how patients present to renal services and how prepared they are for dialysis once they have been referred. This has not been shown before in the UK which provides a free-at-point-of-use health care system. The association with late referral was not shown in the UK Renal Registry report of 2003 (UK Renal Registry 2003), but was reported in subsequent analysis in 2006 *(Caskey et al. 2006).* SIRS collaborated to give data to both these studies, to allow social deprivation across the UK to be reported. Further work needs to be done to suggest whether this delayed presentation is due patient non-attendance, practitioner bias or inadequate resources for a more dependent group of patients.

In this study ethnic minorities were more socially deprived. However, the Townsend Index is not validated in people from ethnic minorities. It is possible that families who are less deprived than their neighbours choose to live in certain areas for social reasons and this scoring system would not account for this.

A higher proportion of single status, no spouse or long-term partner, was seen in more socially deprived groups. This finding is likely to have implications for support for treatment in the community.

Our study found increased rates of diabetes in more socially deprived subjects starting RRT. Data from UK Renal Registry found a similar association *(UK Renal Registry 2003).* There was no increase in vascular co-morbidity seen in more socially deprived subjects, despite the increase in vascular disease seen in other patients in the UK. This may either indicate an increased incidence in all patients with ESRD, or a bias in referral or acceptance of socially deprived patients with vascular disease and ESRD or may reflect a higher

incidence of vascular disease in the less socially deprived patients. Consistent with this last point, is that there is also no difference in cigarette smoking noticed between social groups, unlike in the rest of the UK. It is noted, however, that data regarding smoking is incomplete and it may be there is a selection bias in the collection of this data which may have skewed the results.

7.4. Impact of Social Deprivations on Outcomes

Table 7.2. shows the unadjusted and adjusted hazards ratios for social deprivation on outcome (hospitalisation, mortality and transplantation), using Cox Regression analysis.

Table 7.2. Odds ratios for social deprivation (Townsend score) on outcomes

	Unadjusted Odds Ratio *(95% CI)*	**Adjusted Odds Ratio**[δ] *(95% CI)*
Hospitalisation	**1.01** ***(0.99-1.03)***	**1.02** ***(0.99-1.05)***
Mortality	**1.0** ***(0.97-1.03)***	**1.01** ***(0.96-1.07)***
Transplantation	**0.97** ***(0.92-1.02)***	**0.96** ***(0.9-1.03)***

[δ]***Adjusted for age, sex, race, marital status, primary renal diagnosis, vascular co-morbidity, mode of presentation and centre***

Socioeconomic status was not an independent predictor of mortality in our study. It was also not predictive of rates of transplantation once on the RRT program. In our study, social deprivation was not an independent predictor of hospitalisation, when marital status was added as a co-factor, reflecting the impact of poor social support on increased hospital stays.

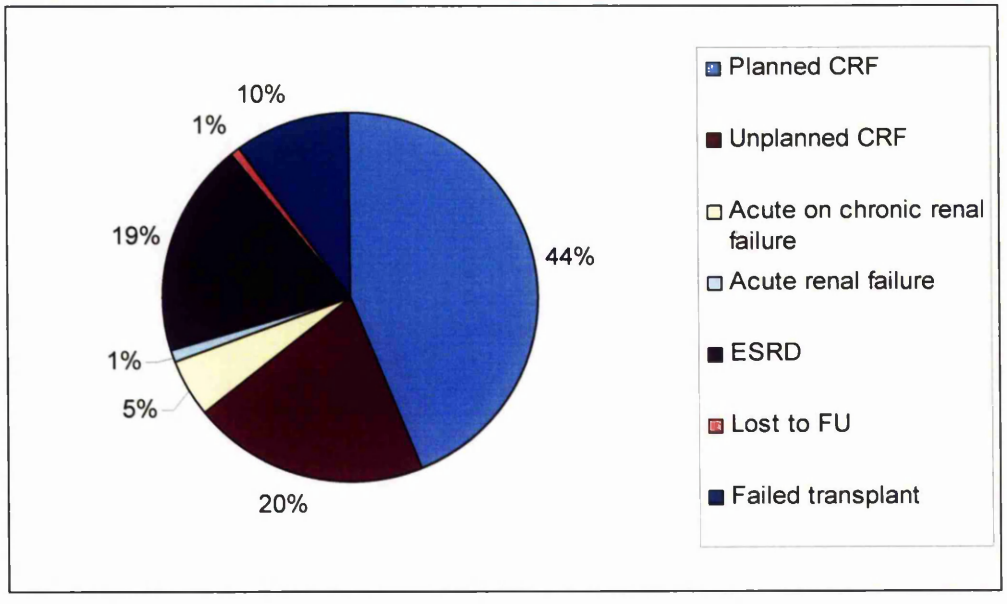
Chapter 8: Impact of Mode of Presentation and on Outcomes in patients with End Stage Renal Disease

Patients with ESRD present to renal services in different ways and times. There is no clear definition of late referral or emergency dialysis and consequently different definitions exist *(UK Renal Registry. Sixth Annual Report 2003).* The SIRS was a prospective design and patients were entered as they started RRT. Data regarding presentation was recorded using a variable defined à priori, combining a time period of 1 month (to indicate early and late referral), provision of planned suitable access (to indicate unplanned dialysis) and speed of renal deterioration (acute, chronic and unknown) The definitions are shown in detail in table 3.4.

8.1. Frequency of mode of presentation

This is shown in graph 8.1.

Graph 8.1. Distribution of mode of presentation in the SIRS population



In the SIRS population, 68.9% of patients new to RRT were seen by renal services at least one month prior to starting dialysis. They were further divided into a planned chronic renal

failure group, where appropriate dialysis access was created prior to starting RRT and those without access, the unplanned group, compromising 43.8% and 20.4% of the cohort, respectively. 10% of patients were failed transplants. 20.0% of the cohort presented to renal services less than a month prior to requiring RRT, of these the largest group are patients who present with end stage renal failure (18.9%).

Patients who present as acute on chronic renal failure (where there is an unexpected decline in renal function often secondary to intercurrent illness), with acute renal failure and lost to follow-up, form less than 7% of total cohort. These groups are too small for meaningful analysis and were excluded from subsequent analyses to prevent large errors in reporting the data.

8.2. Factors independently predicting mode of presentation to renal services

In table 8.1 the results of a multinomial regression analysis are presented. This was done to study the independent predictors of presenting for RRT in different ways. Planned CRF is the reference category against which the other groups are compared.

Table 8.1. Predictors of different modes of presentation (reference category is planned chronic renal failure)

	Failed Transplants AOR$^{\delta}$ (95% CI)	Late Referrals AOR$^{\delta}$ (95% CI)	Unplanned CRF AOR$^{\delta}$ (95% CI)
Age	0.97**** (0.95-0.99)	1.01 (1.00-1.03)	1.03**** (1.01-1.04)
Female gender	0.73 (0.43-1.24)	0.57*** (0.39-0.85)	0.86 (0.58-1.28)
White	1.48 (0.64-3.44)	0.64 (0.36-1.11)	0.95 (0.51-1.78)
Townsend Score	1.04 (0.98-1.11)	1.05* (1.01-1.10)	1.08*** (1.03-1.13)
No vascular disease	0.77 (0.41-1.44)	0.94 (0.62-1.42)	0.84 (0.55-1.28)
Marital Status			
Married	1 (reference category)	1 (reference category)	1 (reference category)
Single	0.85 (0.41-1.74)	1.43 (0.83-2.47)	2.58*** (1.51-4.41)
Divorced	1.56 (0.55-4.43)	1.69 (0.75-3.81)	2.34* (1.10-4.94)
Widowed	1.31 (0.45-3.82)	1.43 (0.77-2.66)	1.03 (0.52-2.07)
Renal diagnosis			
Glomerulonephritis	1 (reference category)	1 (reference category)	1 (reference category)
Interstitial nephropathy	1.03 (0.50-2.09)	0.75 (0.38-1.46)	0.72 (0.40-1.31)
RVD	1.44 (0.44-4.72)	1.43 (0.62-3.29)	0.51 (0.22-1.16)
Diabetic nephropathy	0.18** (0.05-0.65)	1.59 (0.83-3.08)	1.25 (0.69-2.26)
Other multisystem	0.84 (0.29-2.46)	2.95*** (1.46-5.98)	0.55 (0.22-1.34)
Unknown	1.20 (0.58-2.49)	2.37*** (1.29-4.35)	0.72 (0.40-1.31)
Centre			
Satellite	1 (reference category)	1 (reference category)	1 (reference category)
Hope	1.14 (0.29-4.42)	2.71 (0.89-8.32)	1.57 (0.59-4.18)
MRI	5.19** (1.44-18.73)	3.81** (1.24-11.67)	2.83* (1.07-7.49)
Preston	1.12 (0.29-4.42)	4.42** (1.45-13.51)	1.97 (0.73-5.31)
Withington	2.37 (0.48-11.77)	6.67*** (1.78-25.06)	5.34** (1.63-17.46)

$^{\delta}$*Adjusted for age, gender, ethnicity, Townsend score, vascular co-morbidity, marital status, renal diagnosis and centre.*

**p < 0.05; **p < 0.01; ***p<0.005; ****p<0.0001*

There was no independent association between late referral and age, vascular co-morbidity and ethnicity. Male patients were more likely to be referred late. It may be that older patients are not referred or accepted for RRT, and the relatively young age and of the SIRS cohort may be a result of this bias in referral. Patients with renal disease secondary to other multisystem disorders were likely to be referred late. This is probably because renal disease often occurs late in many multisystem disorders and the progression to ESRD is unpredictable. More patients who present late are likely to have small, scarred kidneys and therefore it is often not possible to diagnose their underlying renal disease. This has implications for future transplantation success and may reflect a missed opportunity to have delayed, or even prevented, the need for RRT. Compared to the Rochdale satellite unit, patients who were started on dialysis in MRI, Preston and Withington presented late. Patients at Hope were either referred early or were less likely to be referred at all or less likely to be accepted for RRT. Given the lower acceptance rates at Hope (shown in table 4.7) it is likely to be a combination of the last 2 reasons. There was an association between more social deprivation and late referral, which may in part explain the high incidence of ESRD seen in patients who are socially deprived.

Patients who started dialysis because their previous transplant failed, are younger, less likely to have diabetic nephropathy and more likely to start dialysis at MRI (which has an acute transplantation service). As transplants function for years the young age and fewer patients with diabetes will reflect transplantation acceptance bias from some years ago. Practice now is shown in chapter 10.

Out of every 3 patients who are referred to renal services prior than a month to needing RRT, 1 will start dialysis without access. These patients are more likely to be older, more socially deprived and more likely to be single or divorced. They are also more likely to be start dialysis at MRI or Withington. The length of referral in months, calculated from date of referral, was compared between the planned CRF and unplanned CRF group, as shorter referral times (but longer than 1 month) may have an impact on dialysis. There was no significant difference between the 2 groups; mean length of follow up prior to RRT was 44.2 months (95% CI 34.2 – 53.8) in the unplanned group and 51.0 months (95% CI 44.5-57.3) in the planned group (p value > 0.05, compared using a one-way ANOVA).

8.3. Biochemical, haematological and treatment factors at initiation of RRT associated with mode of presentation to renal services

Table 8.2. shows the different factors associated with mode of presentation at initiation of RRT. A multinomial regression analysis was done using planned CRF as the reference category. GFR at initiation of dialysis was calculated using the Cockcroft and Gault formula, which uses age, weight and gender as part of the formula. Associations with age and sex are shown below, and weight was not significantly different across the groups. However to exclude any error caused by these variables, when GFR was analysed weight was included in the analysis as a separate variable.

Table 8.2. Adjusted associations with mode of presentation at initiation of dialysis (reference category is planned chronic renal failure)

	Failed Transplants AOR$^{\delta}$ (95% CI)	Late Referrals AOR$^{\delta}$ (95% CI)	Unplanned CRF AOR$^{\delta}$ (95% CI)
Serum Albumin	0.89**** (0.84-0.93)	0.85**** (0.82-0.89)	0.85**** (0.82-0.89)
Haemoglobin	0.97**** (0.95-0.99)	0.96**** (0.95-0.97)	0.96**** (0.95-0.97)
Serum calcium	*Not significant*	0.18**** (0.09-0.33)	0.37*** (0.19-0.73)
Serum phosphate	*Not significant*	2.73**** (2.09-3.56)	2.55**** (1.94-3.34)
Diastolic blood pressure	*Not significant*	*Not significant*	*Not significant*
GFR at start of dialysis$^{\kappa}$	1.08* (1.01-1.16)	0.93* (0.88-0.99)	0.86**** (0.80-0.93)
Haemodialysis	3.84**** (2.22-6.66)	13.25**** (8.42-20.86)	15.86**** (9.66-26.03)
No EPO treatment	*Not significant*	2.50**** (1.65-3.77)	*Not significant*

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, vascular co-morbidity, marital status, renal diagnosis and centre.***

$^{\kappa}$***Adjusted for age, gender, ethnicity, Townsend score, vascular co-morbidity, marital status, renal diagnosis, centre and weight.***

****p < 0.05; **p < 0.01; ***p<0.005; ****p<0.0001***

Patients presenting as failed transplants tend to have lower serum albumin and haemoglobin at initiation of dialysis. This may reflect the impact on health of long term RRT. They have a higher GFR at initiation of dialysis and are much more likely to start haemodialysis (possibly because of patient preference and previous abdominal surgery make PD relatively contra-indicated).

Patients referred to renal services within a month of needing dialysis, have a lower GFR at initiation of dialysis and are much less likely to have received specialised treatment for anaemia or bone disease, e.g. EPO therapy. These 2 factors may explain to some degree why they start dialysis with low haemoglobin, serum calcium and high serum phosphate. They also have a low serum albumin which may reflect poor nutrition or other concurrent illnesses, both of which are exacerbated by a period of uraemia. They are more likely to start haemodialysis.

Patients in the unplanned CRF have access to renal services and there is no difference in EPO prescription, however, as well as starting dialysis without permanent access, they start dialysis with a similar profile to patients referred late. They have a lower GFR at initiation of dialysis, low serum albumin, low haemoglobin, low serum calcium and high serum phosphate. They also are more likely to start haemodialysis and not peritoneal dialysis.

8.4. Impact of mode of presentation on outcome of patients with ESRD

Table 8.3. shows the outcomes of patients presenting in the groups defined above, in terms of time to hospitalisation, mortality and transplantation. The adjusted odds ratios given below were produced by performing Cox regression analysis.

Table 8.3. Outcomes of different modes of presentation to renal services

	Hospitalisation AOR$^{\delta}$ (95% CI)	Mortality AOR$^{\delta}$ (95% CI)	Transplantation AOR$^{\delta}$ (95% CI)
Planned CRF	1 (reference category)	1 (reference category)	1 (reference category)
Unplanned CRF	No significant increased risk	2.31**** (1.62-3.29)	0.29*** (0.13-0.64)
Late referral	1.48*** (1.16-1.89)	2.00**** (1.44-2.76)	0.35*** (0.18-0.69)
Failed Transplants	No significant increased risk	No significant increased risk	0.47* (0.23-0.93)

$^{\delta}$***Adjusted for age, gender, ethnicity, Townsend score, vascular co-morbidity, marital status, renal diagnosis and centre.***

****p < 0.05; **p < 0.01; ***p<0.005; ****p<0.0001***

Failed transplants are less likely to receive another transplant than those patients with a planned start to RRT, who have not had a previous transplant. This is likely to be because of increased difficulty in finding a suitable matched kidney in this group.

Patients referred late are likely to be hospitalised sooner after start of RRT than the other groups. They are also less likely to be transplanted during the study, most likely because they will have spent a shorter time on the transplant waiting list, owing to the delay in transplant work up as they presented late. They also have a higher risk of mortality, which is probably a reflection of their general health as they start RRT.

Patients with an unplanned start to dialysis are much less likely to be transplanted. Similar to patients who are referred late, with whom they share many characteristics at initiation of dialysis, have a higher risk of mortality. This group warrants further investigation to study why they present for dialysis so late. It may be physician bias or inadequate haemodialysis resources, but patient non-acceptance of the reality or need for dialysis is also likely to be a contributory factor. Further studies designed to answer this question are required.

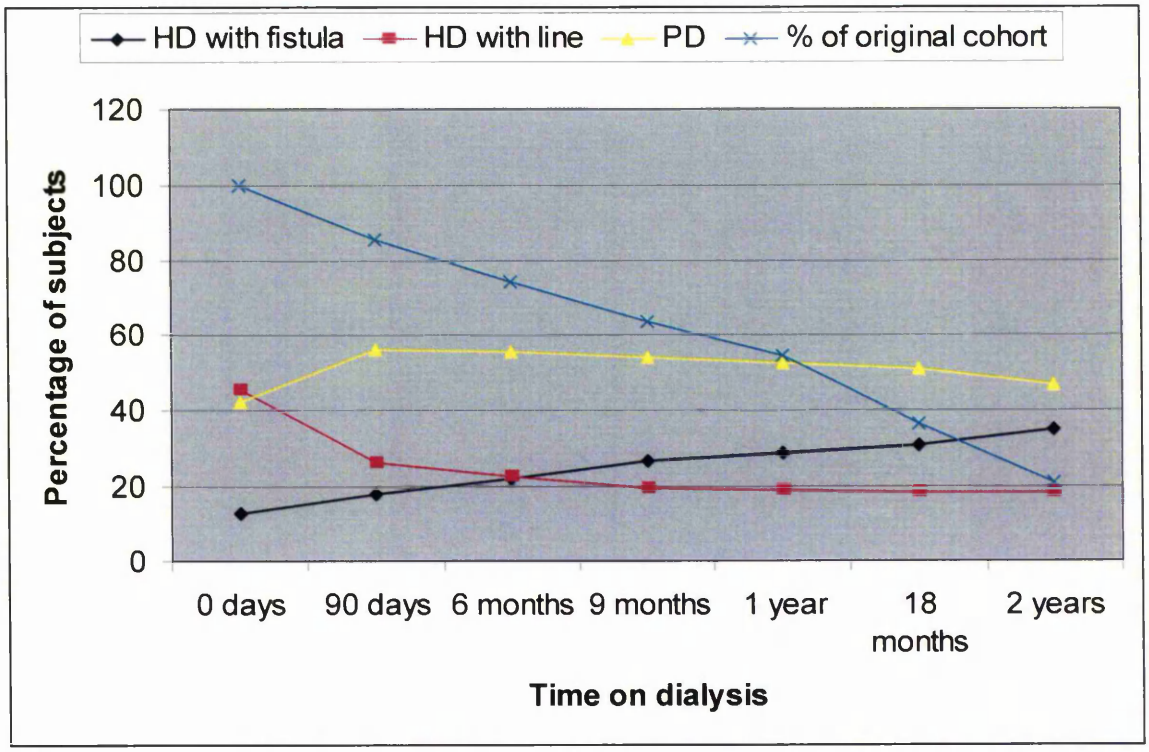
Chapter 9: Impact of dialysis modality in patients with End Stage Renal Disease

As shown in chapter 4 a much greater proportion of the SIRS population are likely to use peritoneal dialysis than the rest of the UK. Further investigation of the associations and outcomes of dialysis modality are carried out in this chapter. Patients using haemodialysis, were further divided into groups depending on the access they were using, as these groups are likely to have different outcomes.

9.1. Frequency of dialysis modality with time

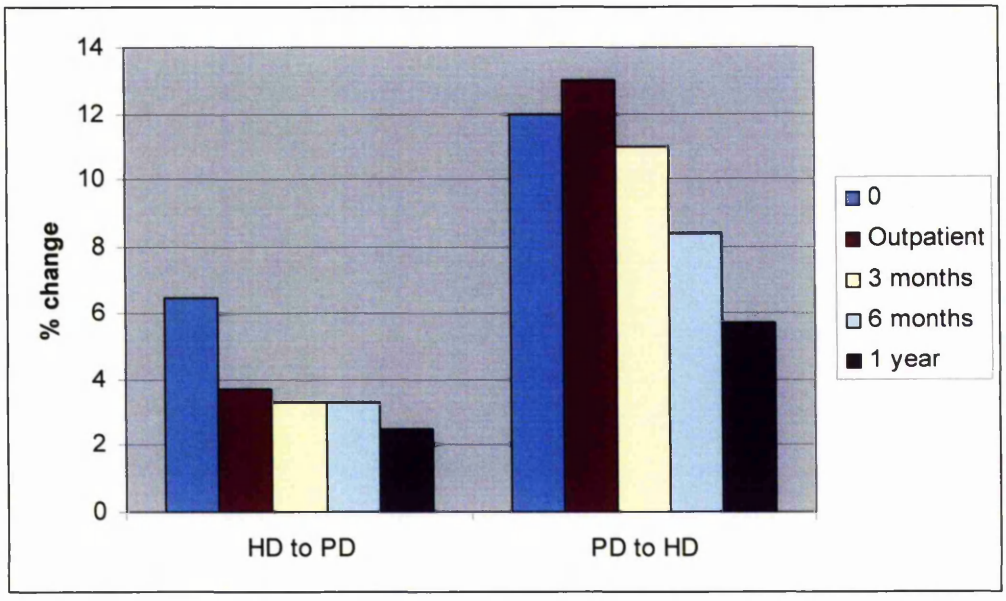
This is shown in graph 9.1.

Graph 9.1. Dialysis modality of the study population over time



Graph 9.1 shows the proportion of patients using peritoneal dialysis declines over time, while those using haemodialysis with a fistula or graft for access increases steadily. The proportion of patients using a line for haemodialysis changes very little after 9 months on RRT, suggesting that permanent access is difficult to create in this group, and a line may be the access of choice.

Graph 9.2. The percentage of subjects who changed dialysis modality, by length of time on each modality.



- The graph above represents 5 different cohorts. Cohort 1 started inpatient dialysis. The 1st bar shows the percentage of cohort 1 who switched dialysis modality (from HD to PD in left hand series and from PD to HD in right hand series). The patients cohort 1 who switched modality were censured from subsequent analysis. Cohort 3 (3 months) represents patients who received at least 90 days of the same dialysis therapy, but subsequently changed modality. Again once a patient changed modality they were removed from subsequent analyses.
- Graph 9.2 shows that of the patients who had at least 90 days of continuous PD (3 months) 11% switched to HD subsequently; of patients who had at least 90 days of continuous HD by day 90, 3.3% switched to PD subsequently. This is comparable with data from the UK Renal Registry 2003, showing an 11.7% switch from PD to HD and 3.2% from HD to PD, using the same definition.
- The rate of change decreases to 1 year, which is perhaps surprising given that PD failure rates increase with time on PD. This suggests a number of patients were started on PD inappropriately and failed early.
- Switching from peritoneal dialysis to haemodialysis was 2.5 times more likely than changing from HD to PD (AOR 2.49 [95% CI 1.5-4.0], $p<0.001$).

- Males were more likely to switch from PD to HD (AOR 1.87 [95% CI 1.15-3.0], p=0.01) than females who start PD. This may be because they get inadequate dialysis with PD, given their increased body surface area and muscle bulk compared with females.
- Patients referred late were less likely to change from HD to PD (AOR 0.55 [95% CI 0.32-0.95], p<0.03). This may reflect patients who are referred early are more likely to choose PD, but may require a period of emergency HD before they can be established on PD.

Table 9.1. shows that changing therapy from peritoneal dialysis to haemodialysis results in lower mortality (compared with patients who stay on peritoneal dialysis), but consumes more resources such as hospitalisation.

Table 9.1. Impact of therapy change from peritoneal dialysis to haemodialysis on patient outcomes, using Cox regression analysis

	Mortality AOR$^{\delta}$ (95% CI)	Hospitalisation AOR$^{\delta}$ (95% CI)
No change from PD	**1 (reference)**	**1 (reference)**
Change from PD to HD	**0.38 (0.18-0.81)** ***p=0.01***	**2.45 (1.72-3.50)** ***p<0.001***

$^{\delta}$***Adjusted for age, sex, ethnic minority, primary renal diagnosis, mode of presentation, serum albumin and centre***

9.3. Factors which predict dialysis modality

Characteristics of patients starting on different modalities as outpatients are summarised in table 9.2. A multinomial regression analysis was performed to ascertain which factors predicted dialysis modality as an outpatient.

Table 9.2. Adjusted odds ratio for factors associated with different dialysis modalities, *HD with a fistula was the reference category.*

	HD with line	PD
	AOR$^{\delta}$ (95% CI)	AOR$^{\delta}$ (95% CI)
Age	1.00 (0.99-1.02)	0.99 (0.98-1)
Female sex	0.81 (0.51-1.29)	0.67 (0.43-1.05)
White ethnicity	1.41 (0.68-2.93)	0.96 (0.46-1.98)
Townsend Score	1.0 (0.93-1.07)	0.98 (0.92-1.04)
Vascular co-morbidity	1.03 (0.62-1.71)	0.99 (0.6-1.63)
Albumin	0.97 (0.93-1.02)	1.04 (0.99-1.08)
Renal diagnosis		
Glomerulonephritis	1 (reference category)	1 (reference category)
Interstitial nephropathy	0.47 (0.20-1.11)	0.41* (0.19-0.89)
RVD	1.33 (0.49-3.66)	3.66 (0.21-1.6)
Diabetic nephropathy	1.31 (0.59-2.9)	2.90 (0.37-1.73)
Other multi-system	1.16 (0.46-2.91)	2.91 (0.2-1.24)
Unknown	0.99 (0.46-2.14)	2.14 (0.31-1.33)
Mode of presentation		
Planned CRF	1 (reference category)	1 (reference category)
Unplanned CRF	17.46** (8.24-36.97)	0.54 (0.26-1.15)
Late referral	47.72** (17.3-131.0)	1.78 (0.65-4.84)
Failed transplant	2.04 (0.92-4.52)	0.37* (0.18-0.75)
Centre		
Satellite	1 (reference category)	1 (reference category)
Hope	2.43 (0.87-6.79)	4.00** (1.81-8.85)
MRI	4.62* (1.60-13.37)	10.26** (4.46-23.61)
Preston	2.10 (0.73-6.05)	5.04** (2.31-10.99)
Withington	1.40 (0.40-4.88)	1.56 (0.56-4.35)

$^{\delta}$Adjusted for age, sex, ethnicity, Townsend score, primary renal diagnosis, vascular co-morbidity, late referral, serum albumin and centre.

$*p < 0.05$; $**p < 0.001$

Table 9.2 shows:

- There is a centre effect, with patients starting dialysis at MRI most likely to start peritoneal dialysis.
- Peritoneal dialysis is less likely to be initial therapy for patients with interstitial nephropathy (the commonest single disease aetiology causing ERSD is adult polycystic kidney disease in this group. In this condition the abdomen can become distended with large polycystic kidneys, therefore this can be a relative contra-indication to PD).
- PD is also less likely to be commenced in patients who present with failing transplants. Abdominal surgery is a relative contra-indication to PD as the peritoneal membrane may have been damaged.
- Starting haemodialysis with a line is strongly associated with late referrals. Patients at MRI are also more likely to start haemodialysis with a line.
- The table above shows that there were no particular groups, i.e. younger patients, ethnic groups or less socially deprived patients, who were associated with a particular type dialysis. In the rest of the UK, where PD forms a much lower proportion of dialysis therapy, younger and less socially deprived patients were more likely to start PD *(UK Renal Registry. Sixth Annual Report. 2003).*

9.4. Impact of dialysis modality on outcomes of patients with ESRD

Table 9.3. shows the adjusted odds ratios for mortality for initial therapy using Cox regression analysis, and for therapy over 2 years using time dependent analysis, which reflects the last mode of therapy noted at follow up prior to death. Table 9.3 gives the adjusted odds ratios for different outcomes (transplantation, hospitalisation and hospitalisation with sepsis) using Cox regression.

Table 9.3. Adjusted odds ratios for mortality for initial mode of therapy and therapy over first 2 years.

	AOR$^{\delta}$ Mortality (95% CI)
Initial therapy	
HD with fistula	1 (reference category)
HD with line	2.25** (1.31-3.86)
PD	1.74* (1.01-3.01)
Therapy over 2 years	
HD with fistula	1 (reference category)
HD with line	2.37** (1.58-3.58)
PD	1.56* (1.03-2.34)

$^{\delta}$***Adjusted for age, sex, ethnicity, primary renal diagnosis, vascular co-morbidity, mode of presentation, serum albumin and centre.***

****p<0.05; **p<0.05***

Table 9.3 shows increased mortality in patients starting and persisting on haemodialysis with a line and peritoneal dialysis compared with patients using haemodialysis with a fistula.

Table 9.4. Other outcomes for initial mode of therapy

	HD with fistula	HD with line AOR$^{\delta}$ (95% CI)	PD AOR$^{\delta}$ (95% CI)
Transplantation	1 (reference category)	0.78 (0.37-1.64)	1.34 (0.69-2.62)
Hospitalisation	1 (reference category)	1.84** (1.28-2.66)	1.46* (1.01-2.10)
Admission with sepsis	1 (reference category)	4.53** (1.61-12.7)	4.08** (1.45-11.49)

$^{\delta}$***Adjusted for age, sex, ethnicity, primary renal diagnosis, vascular co-morbidity, mode of presentation, serum albumin and centre.***

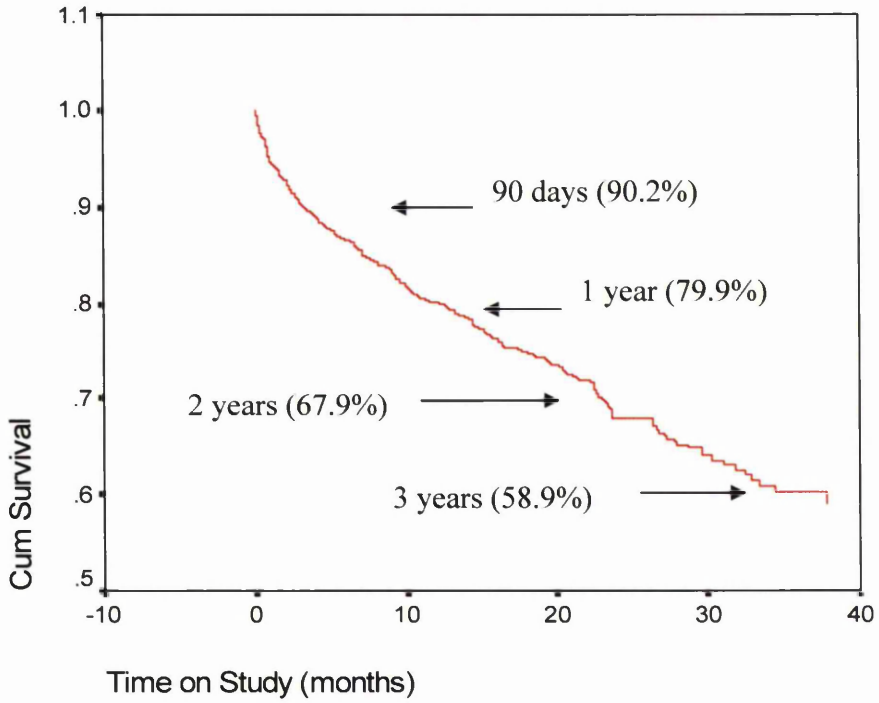
****p<0.05; **p<0.05***

This shows no difference in transplantation rates between the different modalities, but patients starting haemodialysis with a line and those starting PD have higher hospitalisation rates, and particularly higher odds of a hospital admission with sepsis.

Part I: Mortality

There were 292 deaths in the cohort during follow up. The survival curve is shown in graph 10.1. This shows a high mortality rate, especially in the first 90 days after starting dialysis.

Graph 10.1. Survival curve of the whole study population



The survival curve for the cohort is steepest in the first 90 days after starting dialysis, giving an unadjusted survival of 90.2%. This is consistent with data from UK Renal Registry which quotes a 90% first 90 day survival *(UK Renal Registry. Sixth Annual Report. 2003)*. The EDTA registry record survival rates only after the patient has survived 90 days of dialysis. Our cohort had a 79.9% survival at 1 year, 67.9% at 2 years and 58.9% at 3 years. This compares with UK registry data of 78%, 69% and 59% at 1, 2 and 3 years respectively. Data from the European Registry shows 87% survival at 1 year and 77% survival at 2 years, after excluding the patients who died in the first 90 days of dialysis *(EDTA-ERA Renal Registry 2002 Annual Report)*. Data from the DOPPS study suggested that the UK had a higher mortality rate in point prevalent dialysis patients *(Rayner et al. 2004)*, but our study does not find a similar difference in incident patients.

Impact of factors on mortality (unadjusted)

Using Cox proportional hazards regression analysis, an odds ratio for mortality was obtained for each factor collected. The Wald statistic is also shown, which reflects the strength of the association between the factor and mortality. The results are shown in tables 10.1-10.6. The number of patients in each group are shown in the frequency tables 4.3 to 4.10 in chapter 4.

Table 10.1. Unadjusted odds ratios for mortality for demographic factors.

Factor	Odds ratio *(95% CI)*	p-value	Wald
Age	1.05 *(1.04-1.05)*	<0.001	109.3
Gender (female)	1.08 *(0.86-1.35)*	>0.05	0.4
Ethnic Group		>0.05	2.2
White	1.00 *(reference)*		
Asian	0.76 *(0.5-1.15)*	>0.05	1.7
Afro-Caribbean	1.15 *(0.61-2.17)*	>0.05	0.2
Chinese	0.59 *(0.08-4.2)*	>0.05	0.3
Smoking Status		0.07	7.2
Never	1.00 *(reference)*		
Current	1.07 *(0.73-1.58)*	>0.05	0.1
Ex <5 years	1.18 *(0.74-1.88)*	>0.05	0.5
Ex >5 years	1.55 *(1.11-2.16)*	0.01	6.7
Pack years	1.00 *(1-1.01)*	>0.05	1.3
Units of alcohol (per week)	1.00 *(1-1)*	>0.05	0.0
Marital Status		0.01	14.4
Married	1.00 *(reference)*		
Widowed	1.48 *(1.04-2.10)*	0.03	4.8
Separated	1.02 *(0.38-2.74)*	>0.05	0.0
Single	0.63 *(0.44-0.89)*	0.009	6.7
Divorced	1.16 *(0.69-1.97)*	>0.05	0.3
Co-habits	0.76 *(0.24-2.39)*	>0.05	0.2

Table 10.2. Unadjusted odds ratios for mortality for referral data and renal diagnosis

Factor	Odds ratio *(95% CI)*	p-value	Wald
Creatinine at referral	1.00 *(1.0-1.0)*	>0.05	0.0
Source of referral		>0.05	4.6
GP	1.00 *(reference)*		
A&E	1.08 *(0.54-2.19)*	>0.05	0.0
Hospital transfer	1.38 *(1.01-1.9)*	0.05	3.8
Diabetic clinic	1.56 *(0.83-2.9)*	>0.05	1.9
Hospital consultant	1.21 *(0.86-1.7)*	>0.05	1.2
Mode of presentation		<0.001	68.7
Planned chronic renal failure	1.00 *(reference)*		
Unplanned chronic renal failure	2.46 *(1.83-3.3)*	<0.001	36.2
Acute renal failure	4.15 *(2.01-8.56)*	<0.001	14.9
Acute on chronic renal failure	3.15 *(2.01-4.95)*	<0.001	24.9
End stage renal failure	2.38 *(1.76-3.23)*	<0.001	31.3
Lost to follow up	2.61 *(1.06-6.44)*	0.04	4.4
Failed transplant	0.90 *(0.55-1.48)*	>0.05	0.2
Length of referral	0.99 *(0.99-1.0)*	<0.001	18.0
Primary Renal Diagnosis		<0.001	56.6
Renal Specific disease	1.00 *(reference)*		
Renovascular	1.99 *(1.3-3.06)*	0.002	10.0
Diabetic nephropathy	2.11 *(1.53-2.89)*	<0.001	21.2
Myeloma	8.17 *(4.44-15.05)*	<0.001	45.4
Other multisystem	2.14 *(1.44-3.19)*	<0.001	14.2
Unknown	1.78 *(1.3-2.43)*	<0.001	13.0

Table 10.3. Unadjusted odds ratios for mortality for dialysis modality, access and centre

Factor	Odds ratio *(95% CI)*	p-value	Wald
Mode RRT (on discharge)		<0.001	30.4
CAPD	1.00 *(reference)*		
HD	2.00 *(1.56-2.56)*	<0.001	30.2
Transplant	0.00 *(0-0)*	>0.05	0.0
Intermittent PD	1.47 *(0.82-2.62)*	>0.05	1.7
APD	1.39 *(0.78-2.49)*	>0.05	1.3
Access (on discharge)		<0.001	124.0
Tenckhoff	1.00 *(reference)*		
Temporary internal jugular line	2.68 *(1.81-3.97)*	<0.001	24.1
Temporary subclavian line	0.00 *(0-0)*	>0.05	0.0
Temporary femoral line	14.62 *(8.77-24.4)*	<0.001	106.0
Semi-permanent internal jugular line	1.80 *(1.35-2.40)*	<0.001	15.8
Semi-permanent subclavian line	0.97 *(0.14-6.97)*	>0.05	0.0
AV fistula - radial	1.10 *(0.56-2.16)*	>0.05	0.1
AV fistula - brachial	1.09 *(0.72-1.64)*	>0.05	0.2
Graft	0.75 *(0.11-5.39)*	>0.05	0.1
Centre		0.006	14.6
MRI	1.00 *(reference)*		
Hope	1.10 *(0.81-1.49)*	>0.05	0.3
Preston	1.36 *(1.04-1.78)*	0.03	5.1
Withington	0.78 *(0.47-1.32)*	>0.05	0.8
Satellite	0.50 *(0.26-0.96)*	0.04	4.3

Table 10.4. Unadjusted odds ratios for mortality for anthropometric and laboratory data at initiation of dialysis

Factor	Odds ratio *(95% CI)*	p-value	Wald
Serum sodium	0.96 *(0.94-0.99)*	0.001	10.7
Serum potassium	0.86 *(0.76-0.97)*	0.015	6.0
Serum creatinine	1.00 *(1.0-1.0)*	<0.001	26.0
Serum urea	1.01 *(1.0-1.02)*	0.02	5.5
Serum bicarbonate	1.01 *(0.99-1.03)*	>0.05	0.5
Serum calcium	0.84 *(0.59-1.20)*	>0.05	0.9
Serum phosphate	1.17 *(1.02-1.34)*	0.02	5.3
PTH	1.00 *(1.0-1.0)*	0.02	5.6
Serum albumin	0.93 *(0.91-0.94)*	<0.001	97.4
Haemoglobin	1.00 *(0.99-1.0)*	>0.05	2.2
Serum ferritin	1.00 *(1.0-1.0)*	<0.001	40.0
Serum iron	0.92 *(0.88-0.96)*	<0.001	15.1
Total iron binding capacity	0.96 *(0.93-0.98)*	<0.001	16.3
Iron saturation	0.98 *(0.96-0.99)*	0.01	6.6
Cholesterol	0.86 *(0.77-0.96)*	0.009	6.8
Weight	0.99 *(0.98-1.0)*	0.01	6.7
Systolic BP	0.99 *(0.99-1.0)*	<0.001	12.7
Diastolic BP	0.97 *(0.97-0.98)*	<0.001	44.7

Table 10.5. Unadjusted odds ratios for mortality for co-morbid illnesses

Factor	Odds ratio *(95% CI)*	p-value	Wald
Diabetes		0.001	16.1
Non-diabetic patients	1.00 *(reference)*		
Type 1	1.54 *(1.15-2.06)*	0.003	8.5
Type 2	1.69 *(1.23-2.33)*	0.001	10.4
Unspecified	1.67 *(0.42-6.73)*	>0.05	0.5
CCF (NYHA)		<0.001	44.7
Nil	1.00 *(reference)*		
Grade 1	1.83 *(1.07-3.13)*	0.03	4.8
Grade 2	1.37 *(0.44-4.27)*	>0.05	0.3
Grade 3	1.87 *(0.7-5.02)*	>0.05	1.5
Grade 4	4.36 *(2.77-6.88)*	<0.001	40.2
MI <3 months	2.67 *(1.42-5.02)*	0.002	9.3
MI >3 months	1.95 *(1.39-2.74)*	<0.001	14.9
Angina (NYHA)		<0.001	22.2
Nil	1.00 *(reference)*		
Grade 1	1.45 *(0.89-2.37)*	>0.05	2.2
Grade 2	2.05 *(1.05-3.98)*	0.035	4.5
Grade 3	2.11 *(1.25-3.55)*	0.005	7.9
Grade 4	2.95 *(1.52-5.74)*	0.001	10.2
CABG/Angioplasty	1.93 *(1.33-2.80)*	<0.001	12.1
Peripheral Vascular disease (SVS)	1.00 *(reference)*	<0.001	44.3
Nil			
Grade 1	0.94 *(0.23-3.79)*	>0.05	0.0
Grade 2	1.45 *(0.86-2.44)*	>0.05	1.9
Grade 3	2.70 *(1.73-4.22)*	<0.001	19.2
Grade 4	3.69 *(2.26-6.03)*	<0.001	27.2
Ischaemic ulcers	2.55 *(1.56-4.15)*	<0.001	14.1
Amputation	2.59 *(1.54-4.36)*	<0.001	12.9
Non-coronary angioplasty	4.80 *(2.26-10.17)*	<0.001	16.7
Cerebrovascular disease	1.53 *(1.06-2.22)*	0.02	5.1
Hemiplegia	1.17 *(0.6-2.28)*	>0.05	0.2
Dementia	2.76 *(0.88-8.6)*	0.08	3.1
COPD	1.36 *(0.97-1.9)*	0.07	3.2
Congenital abnormalities	0.69 *(0.26-1.84)*	>0.05	0.6
Connective tissue disorders	1.68 *(1.0-2.82)*	0.05	3.9
Liver disease (non-viral)	1.96 *(0.87-4.4)*	>0.05	2.7
Viral hepatitis	0.78 *(0.35-1.76)*	>0.05	0.4
Peptic ulcer disease	2.42 *(1.33-4.42)*	0.004	8.3
HIV	0.47 *(0.12-1.92)*	>0.05	1.1
Leukaemia	0.63 *(0.16-2.54)*	>0.05	0.4
Lymphoma	0.05 *(0.0-35.4)*	>0.05	0.8
Solid tumour	2.06 *(1.4-3.04)*	<0.001	13.3
Parathyroidectomy	1.81 *(0.9-3.65)*	>0.05	2.7

Table 10.6. Unadjusted odds ratios for mortality for medical treatment

Factor	Odds ratio *(95% CI)*	p-value	Wald
EPO	0.83 *(0.66-1.05)*	>0.05	2.4
EPO dose	1.00 *(1.0-1.0)*	>0.05	1.6
Parenteral iron	0.61 *(0.42-0.90)*	0.01	6.4
Oral Iron	0.75 *(0.57-0.97)*	0.03	4.6
Statin	0.96 *(0.75-1.22)*	>0.05	0.1
Antihypertensives		0.001	21.0
0	1.00 *(reference)*		
1	0.74 *(0.56-0.99)*	0.04	4.1
2	0.56 *(0.41-0.77)*	<0.001	13.2
3	0.46 *(0.3-0.7)*	<0.001	13.4
4	0.49 *(0.25-0.98)*	0.04	4.1
5	0.50 *(0.07-3.57)*	>0.05	0.5

Factors which independently predict mortality in patients with ESRD

A series of analyses were done, using Cox proportional hazards regression, to assess the impact of all the other factors on mortality, with age, gender, ethnicity, primary renal diagnosis and vascular co-morbidity as co-variates. In this manner adjusted odds ratios were obtained. Continuous variables were assessed as continuous variables and as quintiles, to allow assessment of the impact of the extremes of the curves. The results are summarised below, in tables 10.7-10.12.

Table 10.7. Adjusted odds ratios for mortality risk

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Age	1.04 *(1.03-1.05)*	<0.001	65.66
Gender (female)	1.08 *(0.85-1.37)*	>0.05	0.39
Ethnic group		>0.05	1.40
White	1.00 *(reference)*		
Asian	0.91 *(0.59-1.41)*	>0.05	0.19
Black	1.37 *(0.72-2.6)*	>0.05	0.94
Chinese	0.63 *(0.09-4.55)*	>0.05	0.20
Primary Renal Diagnosis		<0.001	24.40
Renal specific	1.00 *(reference)*		
Renovascular	1.17 *(0.75-1.83)*	>0.05	0.48
Diabetes	1.55 *(1.11-2.17)*	0.01	6.66
Myeloma	4.50 *(2.39-8.47)*	<0.001	21.71
Other multi-system	1.47 *(0.96-2.25)*	0.08	3.08
Unknown	1.31 *(0.94-1.82)*	>0.05	2.50
Vascular co-morbidity[λ]	1.75 *(1.38-2.23)*	<0.001	21.13

[δ]***Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity***

[λ]***Includes ischaemic heart disease, peripheral vascular disease and cerebrovascular disease***

Table 10.8. The impact of late referral and mode of presentation on mortality

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Creatinine at referral	1.00 *(1.0-1.0)*	0.04	4.08
Mode of presentation		<0.001	42.37
Planned chronic renal failure	1.00 *(reference)*		
Unplanned chronic renal failure	2.30 *(1.69-3.12)*	<0.001	28.46
Acute renal failure	2.07 *(0.94-4.57)*	0.07	3.26
Acute on chronic renal failure	2.91 *(1.81-4.68)*	<0.001	19.52
End stage renal failure	2.10 *(1.52-2.89)*	<0.001	20.39
Lost to follow up	2.39 *(0.96-5.92)*	0.06	3.52
Failed transplant	1.25 *(0.73-2.16)*	>0.05	0.66
Late referral	1.45 *(1.11-1.89)*	0.006	7.56

[δ]*Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity*

Table 10.9. The impact of dialysis access on mortality

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Access		<0.001	115.91
Tenckhoff	1.00 *(reference)*		
Temporary internal jugular line	2.28 *(1.48-3.5)*	<0.001	14.01
Temporary femoral line	19.07 *(10.79-33.7)*	<0.001	103.07
Semi-permanent internal jugular line	1.29 *(0.93-1.78)*	>0.05	2.35
Semi-permanent subclavian line	0.62 *(0.09-4.57)*	>0.05	0.22
AV fistula - radial	0.71 *(0.35-1.47)*	>0.05	0.84
AV fistula - brachial	0.93 *(0.6-1.45)*	>0.05	0.10
Graft	0.56 *(0.08-4.01)*	>0.05	0.34
Line access	2.09 *(1.38-3.16)*	<0.001	12.19

[δ]*Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity*

Table 10.10. Biochemical factors predictive of mortality

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Serum Sodium	0.97 *(0.95-0.99)*	0.01	6.33
Serum Sodium levels (mmol/l)		<0.001	24.35
>140	1.00 *(reference)*		
138-140	0.73 *(0.5-1.04)*	0.08	3.00
135-137	1.03 *(0.72-1.46)*	>0.05	0.03
<135	1.58 *(1.14-2.19)*	0.006	7.60
Serum Creatinine	1.00 *(1.0-1.0)*	0.01	6.45
Serum Creatinine levels (μmol/l)		>0.05	5.80
>1034	1.00 *(reference)*		
802-1034.5	1.24 *(0.87-1.78)*	>0.05	1.43
618-802	1.41 *(0.99-2.02)*	0.055	3.68
<618	1.51 *(1.06-2.15)*	0.02	5.26
Serum Phosphate	1.26 *(1.11-1.44)*	0.001	11.75
Serum Phosphate levels (mmol/l)		0.003	14.23
<1.75	1.00 *(reference)*		
1.75-2.17	1.18 *(0.83-1.67)*	>0.05	0.82
2.18-2.79	1.69 *(1.2-2.37)*	0.003	9.06
>2.79	1.71 *(1.22-2.39)*	0.002	9.75
Serum Albumin	0.92 *(0.91-0.94)*	<0.001	75.76
Serum Albumin levels (g/l)		<0.001	70.04
>40	1.00 *(reference)*		
35-39	2.50 *(1.44-4.36)*	0.001	10.51
30-34	4.54 *(2.66-7.74)*	<0.001	30.80
<30	6.73 *(3.95-11.48)*	<0.001	49.12

[δ]*Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity*

Table 10.11. Haematological factors predictive of mortality

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Haemoglobin	0.99 (0.99-1.00)	>0.05	0.60
Serum Ferritin	1.01 *(1.01-1.02)*	<0.001	36.59
Serum Ferritin levels (µg/l)		>0.05	6.25
<104	1.00 *(reference)*		
104-179	1.20 *(0.75-1.9)*	>0.05	0.57
180-323	1.19 *(0.75-1.9)*	>0.05	0.53
>323	1.67 *(1.08-2.59)*	0.02	5.22
Serum Iron	0.95 *(0.91-0.99)*	0.02	5.29
Serum Iron levels (µg/dl)		0.06	7.44
>14	1.00 *(reference)*		
11-14	1.43 *(0.65-3.15)*	>0.05	0.80
8-10	1.21 *(0.53-2.77)*	>0.05	0.21
<8	2.25 *(1.1-4.6)*	0.03	4.94
Total iron binding capacity	0.96 *(0.94-0.99)*	0.002	10.02
TIBC levels (µg/dl)		0.01	10.90
>50	1.00 *(reference)*		
43-50	1.59 *(0.7-3.58)*	>0.05	1.23
37-42	2.51 *(1.17-5.39)*	0.02	5.54
<37	2.94 *(1.44-6.01)*	0.003	8.71

[δ]*Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity*

Table 10.12 The impact of weight and blood pressure on mortality

Factor	Adjusted odds ratio[δ] *(95% CI)*	p-value	Wald
Weight	0.98 *(0.97-0.99)*	<0.001	13.61
Weight groups (Kg)		0.002	14.69
>81	1.00 *(reference)*		
69.6-81	1.10 *(0.74-1.62)*	>0.05	0.23
59.6-69.5	1.32 *(0.88-1.97)*	>0.05	1.79
<59.6	2.02 *(1.35-3.01)*	0.001	11.76
Systolic BP	0.99 *(0.99-1.0)*	<0.001	13.32
Systolic BP levels (mmHg)		0.007	11.99
>160	1.00 *(reference)*		
145-160	0.92 *(0.64-1.32)*	>0.05	0.21
131-144	1.22 *(0.85-1.76)*	>0.05	1.16
<131	1.54 *(1.12-2.10)*	0.007	7.20
Diastolic BP	0.98 *(0.98-0.99)*	<0.001	14.99
Diastolic BP levels (mmHg)		0.005	12.75
>90	1.00 *(reference)*		
81-90	1.18 *(0.77-1.82)*	>0.05	0.58
69-80	1.04 *(0.69-1.56)*	>0.05	0.03
<69	1.68 *(1.12-2.51)*	0.01	6.36

[δ]*Adjusted for age, gender, ethnic group, primary renal diagnosis and vascular co-morbidity*

Age was highly predictive of mortality in unadjusted and adjusted analyses. Gender and ethnicity did not predict survival. Myeloma and renovascular disease were responsible for a reasonable proportion of ESRD and had a significant impact on mortality. Myeloma and diabetic nephropathy were independent predictors of mortality. Renovascular disease was not significant when age and other vascular co-morbidity were factored into the equation.

The presence of most co-morbid conditions is associated with increased mortality, but in particular, severe congestive cardiac failure (NYHA grade 4), symptomatic angina (NYHA grades 2-4), previous MI, previous CABG/angioplasty, peripheral vascular disease causing rest pain or tissue loss (SVS grade 3-4) and cerebrovascular disease. Malignancy was highly predictive of mortality in all groups. Vascular disease (coronary artery disease, cerebrovascular disease and peripheral vascular disease) was the most prevalent co-morbidity and was found to be an independent predictor of mortality.

Single patients had a better and widowed patients a worse survival risk, but this disappeared when adjustment was made for age. Alcohol consumption, which is overall low in this population, did not impact on mortality. In unadjusted analysis current smokers and those who had stopped in the last 5 years did not have an increased risk of mortality compared with patients who had never smoked. Ex-smokers who had stopped >5 years prior to dialysis did have an increased risk of mortality, which disappeared when vascular disease was factored into the model.

The two most important predictors of poor outcome were length of follow up prior to referral and provision of adequate vascular access, i.e. avoidance of dialysis lines, especially temporary lines. Patients referred within 1 month of requiring dialysis had a much poorer survival than patients referred earlier. Patients were also defined a priori into those who had been followed up in nephrology clinics and started dialysis with (planned) or without (unplanned) adequate access. Unplanned patients had a higher risk of mortality when compared with planned patients.

Biochemical factors, performed routinely at all hospitals were studied. Most striking was the impact of albumin, compared with an albumin of 40 g/l and above, patients with levels 35-39 g/l, 30-34 and less than 30 g/l all had higher risk of mortality. Phosphate levels higher than 2.18 mmol/l were predictors of mortality. Starting dialysis with a serum sodium

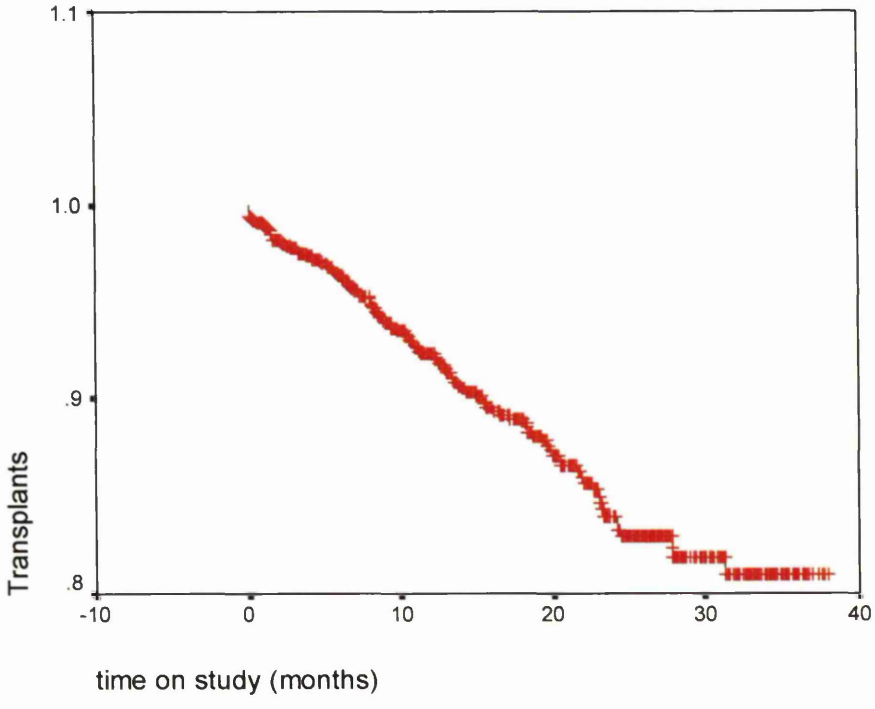
less than 135 mmol/l and a serum creatinine less than 618 μmol/l were independently predictive of mortality, although the effect was modest. Serum urea, bicarbonate and potassium were not predictive of mortality after initiation of RRT. Haemoglobin level at inception of RRT was not predictive of survival in univariate or multivariate analyses. Low serum iron levels less than 8 μg/dl compared with levels greater than 14 μg/dl were independently predictive of mortality, as were total iron binding capacity levels of less than 42 μg/dl compared with levels greater than 50μg/dl. However high serum ferritin levels, greater than 323 μg/l were predictive of mortality compared with levels less than 104 μg/l.

Low body weight at inception of RRT is associated with increased mortality risk. Low blood pressure at the inception of dialysis, independent of known vascular co-morbidity and age, is associated with poor outcomes.

Part II: Transplantation

There were 110 renal transplants during the study period. Figure 10.2. is a Kaplan Meier graph showing the transplants against time. It is almost a linear curve, suggesting that the number of patients assessed and waiting for transplantation exceeds supply at any time point after starting dialysis.

Figure 10.2. Renal transplantation of study population against time



Cox regression analysis was performed to assess which factors were independent predictors of transplantation. The results are shown in table 10.13.

Table 10.13. Adjusted odds ratios for factors associated with transplantation

Factor	Adjusted odds ratio[δ]	95% CI	p-value
Age	0.94	0.92-0.96	<0.001
Gender (female)	1.53	0.94-2.50	>0.05
Ethnicity (Non-white)	0.84	0.40-1.76	>0.05
Townsend Score	0.97	0.92-1.03	>0.05
Marital Status			0.036
Married	1.00 *(reference)*		
Single	0.41	0.22-0.76	0.004
Divorced/Separated	0.59	0.21-1.66	>0.05
Widowed	0	0-0	>0.05
Primary Renal Diagnosis			>0.05
Glomerulonephritis	1.00 *(reference)*		
Interstitial nephritis	0.83	0.46-1.48	>0.05
Diabetic Nephropathy	1.49	0.63-3.56	>0.05
Renovascular disease	0.52	0.23-1.15	>0.05
Other multisystem	0.50	0.18-1.37	>0.05
Unknown	0.57	0.29-1.13	>0.05
Vascular co-morbidity	0.42	0.20-0.88	0.02
Mode of presentation			0.001
Planned CRF	1.00 *(reference)*		
Failed transplant	0.48	0.25-1.01	>0.05
Late referral	0.37	0.19-0.73	0.004
Unplanned CRF	0.29	0.12-0.70	0.005

[δ]*Adjusted for age, sex, ethnicity, Townsend score, marital status, primary renal diagnosis, vascular co-morbidity and mode of presentation.*

Older age is an independent predictor for reduced likelihood of transplantation. This is independent of vascular co-morbidity, which in itself is an independent predictor of reduced likelihood of transplantation. Age was also independent of the presence of any co-morbidities (entered as a separate variable with 0 = no co-morbid conditions and 1 = any co-morbidity) which was entered in another analysis instead of vascular co-morbidity (data not shown). This may be because of physician reluctance to refer for transplantation, patient choice and a lower rate of live related transplantation rates.

Single patients are less likely to get a renal transplant compared with married patients. The reason for this may be lower rates of live related or live unrelated (e.g. from a spouse) transplantation, but further research and data collection are needed to confirm this.

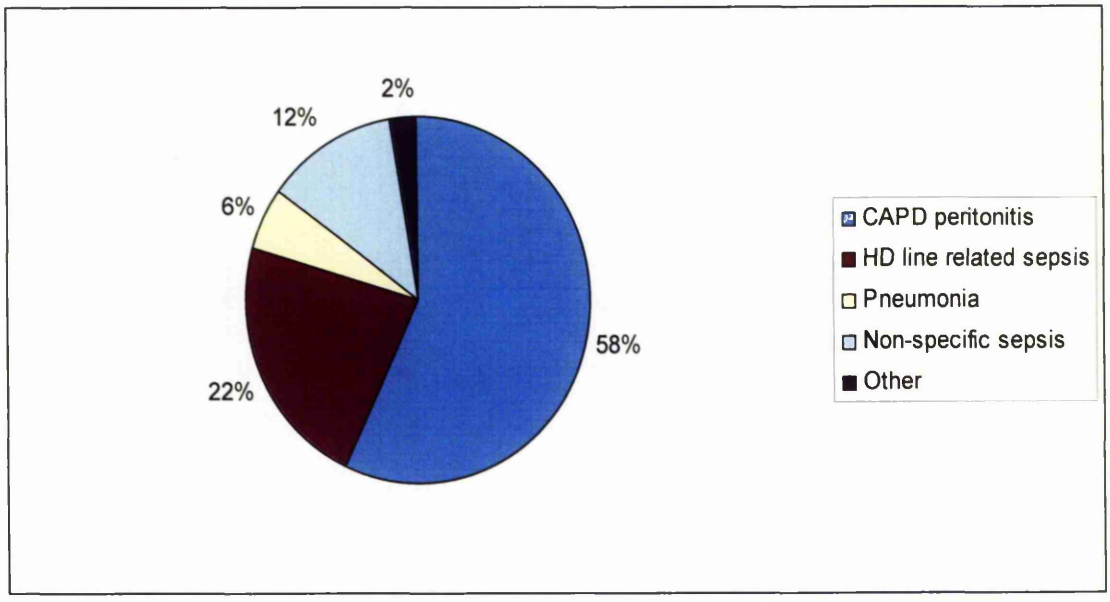
Another important factor affecting transplantation rates is mode of presentation to renal services. Patients with a previous failed transplant did not have significantly reduced rates of subsequent transplantation, once adjustments were made for marital status (compared with analysis in chapter 8). Patients referred late (within a month of requiring dialysis) had lower rates of transplantation. Of note, the group of patients under follow up with renal services but starting dialysis without planned access had significantly lower rates of transplantation. This group are explored in greater detail in chapter 8.

Part III: Hospitalisation

Hospitalisation data has been collected prospectively on the SIRS cohort, with diagnosis, admission and discharge dates noted. Different analyses were carried out for all hospitalisation, and specific hospital admission diagnoses (e.g. myocardial infarction, all cardiovascular admissions etc.). Presented here is the analysis looking at all hospital admissions caused by sepsis.

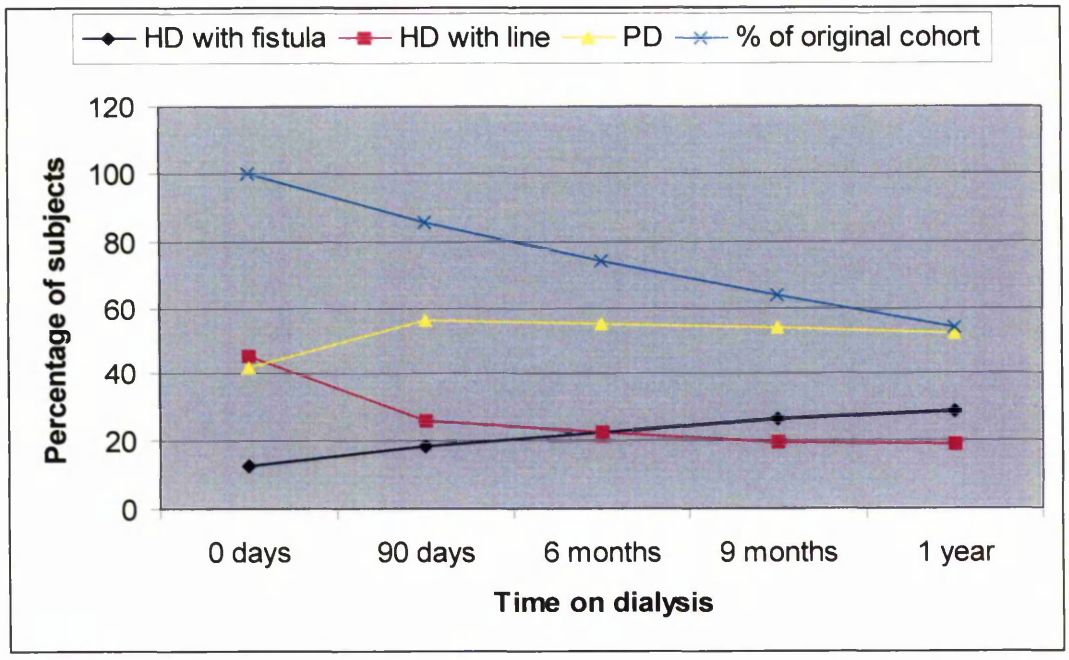
121 patients were admitted with sepsis in a median follow up of 17.7 months (range 0.3-24 months). The causes of their first admission with sepsis are shown in graph 10.3.

Graph 10.3. Causes of first admission with sepsis



CAPD peritonitis accounts for the majority of admissions followed by dialysis line/catheter related infections. Graph 10.4. below shows the different dialysis modalities with time.

Graph 10.4. Dialysis modality of the SIRS cohort against time



As can be seen from the graph, patients on peritoneal dialysis and haemodialysis using a catheter are still 70% of the total cohort at 1 year. Therefore the risk of sepsis is still high.

For further analysis, the sepsis episodes are divided into all sepsis and non-CAPD peritonitis (all sepsis excluding CAPD peritonitis). This was done because CAPD peritonitis is usually a local inflammation and may well have different characteristics to generalised sepsis and, also, given the very high rates of patients on CAPD in the SIRS cohort, our results with such high peritonitis rates may not be applicable to other populations with ESRD. Cox regression analysis was used to show factors independently associated with sepsis, this includes the initial dialysis modality. A time dependent Cox regression analysis was done to assess the dialysis modality immediately prior to hospital admission with sepsis, as patients change modalities with time on RRT.

Table 10.14. Adjusted odds ratios for factors associated with admission with sepsis

Factor	Adjusted odds ratios[δ] for all sepsis	Adjusted odds ratios[δ] for sepsis (non-peritonitis)
Age	0.99 (0.99-1.01)	0.31 (0.99-1.01)
Male	1.28 (0.85-1.91)	1.42 (0.75-2.68)
Ethnicity	1.19 (0.67-2.11)	2.36* (1.14-4.86)
Townsend	0.99 (0.94-1.04)	0.97 (0.9-1.04)
Vascular disease	0.88 (0.57-1.37)	0.66 (0.33-2.48)
Late referral	1.77* (1.14-2.75)	2.35** (1.24-4.45)
Renal Diagnosis		
Glomerulonephritis	1 (reference category)	1 (reference category)
Interstitial nephritis	0.83 (0.43-1.62)	0.96 (0.26-3.65)
Renovascular disease/ hypertension	1.51 (0.7-3.28)	3.32 (0.87-12.69)
Diabetic nephropathy	1.44 (0.77-2.69)	3.41* (1.09-10.66)
Multisystem disorder	1.23 (0.57-2.65)	2.47 (0.69-8.85)
Unknown	0.78 (0.41-1.47)	0.93 (0.27-3.14)
Centre		
Satellite	1 (reference category)	1 (reference category)
Hope	1.31 (0.5-3.47)	0.86 (0.3-2.48)
MRI	0.98 (0.37-2.62)	0.33 (0.1-1.11)
Preston	1.18 (0.45-3.09)	0.40 (0.13-1.21)
Withington	2.2 (0.77-6.29)	0.72 (0.16-3.14)
Initial dialysis modality		
HD with fistula	1 (reference category)	1 (reference category)
HD with line	3.7* (1.31-10.44)	2.0 (0.67-5.97)
PD	3.28* (1.81-9.12)	0.55 (0.16-1.84)
Dialysis modality as a time dependent variable		
HD with fistula	1 (reference category)	1 (reference category)
HD with line	4.41** (1.92-10.1)	3.26** (1.35-7.84)
PD	3.22** (1.47-7.08)	0.55 (0.21-1.48)

[δ]Adjusted for age, sex, ethnicity, Townsend score, renal diagnosis, vascular co-morbidity, late referral, centre and dialysis modality.

**p< 0.05; **p<0.05*

Late referral to renal services (i.e. within 1 month of needing dialysis) is an independent risk factor for a subsequent hospital admission with sepsis, including CAPD peritonitis. The reason for this may be that people referred late are often unwell and have been uraemic for some time. It is known that uraemia affects the immune system, therefore increasing susceptibility to infection.

Patients from ethnic minorities also have a greater risk of non-CAPD peritonitis. There may be several reasons for this; their increased exposure to infectious agents from visiting, or having relatives who have visited, the Indian Subcontinent or they may have more family members living in the same house, increasing risk of transmission of infections.

Haemodialysis with a line is strongly associated with sepsis, whenever it is used during a patient's dialysis career. The fact that if HD with a line as the initial mode of therapy is also associated with all sepsis, including CAPD peritonitis, suggests that many of these patients are switched to CAPD soon after initiation of dialysis. Predictably peritoneal dialysis is strongly associated with CAPD peritonitis, but not other types of sepsis. Patients with diabetic nephropathy have a higher risk of developing sepsis, but not CAPD peritonitis.

Table 10.15 shows the impact an admission with sepsis has on a patient's subsequent mortality risk. Specialised statistical modelling (using SAS package) was used to allow sepsis to be entered as a time dependent variable.

Table 10.15. Unadjusted and adjusted odds ratios for subsequent mortality, in patients admitted with sepsis

	Unadjusted OR	Adjusted OR$^{\delta}$
All sepsis	**1.67* (1.14-2.43)**	**1.72* (1.13-2.6)**
Sepsis (non-peritonitis)	**2.41** (1.53-3.79)**	**2.47** (1.47-4.18)**

$^{\delta}$***Adjusted for age, sex, race, social deprivation, primary renal diagnosis, vascular co-morbidity, late referral, dialysis modality and centre.***

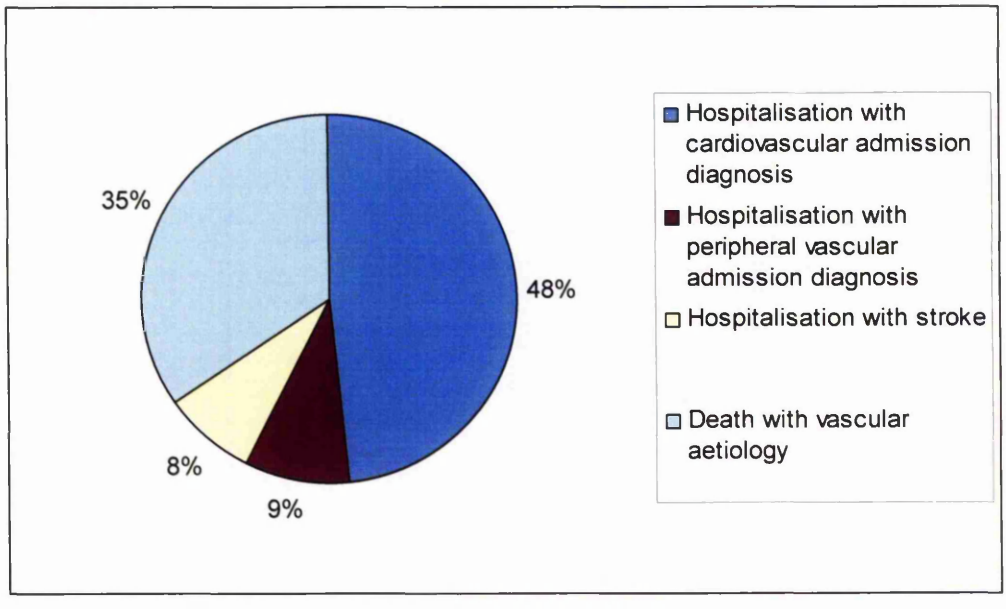
****p < 0.05; ** p < 0.001***

These results show that there is a higher risk of subsequent mortality in patients with ESRD who are admitted with sepsis, but this is higher in patients admitted sepsis which is not CAPD peritonitis.

Part IV: Vascular Disease

Vascular disease is the leading cause of death and morbidity amongst patients with ESRD. Presented here are the factors which predict a vascular event (hospitalisation or mortality on dialysis). The data presented below studies the first major vascular event, whether it is a hospital admission diagnosis or vascular related death. This is because the risk profile for vascular disease changes following a vascular event. Vascular deaths were only entered if there was some objective evidence of a vascular aetiology (e.g. ECG changes or enzyme rise indicating a myocardial infarction), sudden deaths were excluded, although it is accepted that many of these will be caused by a cardiac arrhythmia. There were 124 major vascular events during the study. Figure 10.4 shows what constituted the first vascular event.

Graph 10.5. Causes of first major vascular event



A Cox Regression analysis was performed to look for factors associated with a major vascular event. The results are shown in table 10.16.

Table 10.16. Unadjusted and Adjusted Odds Ratios for a Major Vascular Event

	Unadjusted OR	Adjusted OR[δ]
Age	1.02**** (1.01-1.03)	1.01 (1.00-1.03)
Male Sex	0.91 (0.59-1.39)	1.0 (0.99-1.02)
Ethnic minority	1.02 (0.53-1.97)	0.93 (0.43-2.01)
Townsend Score	1.02 (0.97-1.07)	1.02 (0.97-1.07)
Primary renal diagnosis		
Glomerulonephritis	1 (reference category)	1 (reference category)
Interstitial nephropathy	1.56 (0.76-3.19)	1.26 (0.58-2.76)
Diabetic Nephropathy	2.62** (1.17-5.86)	1.56 (0.64-3.84)
Renovascular disease	2.65*** (1.35-5.20)	1.73 (0.83-3.64)
Other multisystem	1.77 (0.79-3.96)	1.25 (0.50-3.14)
Unknown	1.63 (0.81-3.27)	1.25 (0.59-2.64)
Vascular co-morbidity	2.79**** (1.94-3.94)	2.22**** (1.51-3.26)
Mode of presentation		
Planned CRF	1 (reference category)	1 (reference category)
Unplanned CRF	1.86** (1.17-2.95)	1.87** (1.11-3.14)
Late referral	1.81** (1.16-2.81)	1.65 (0.99-2.79)
Failed transplants	0.83 (0.39-1.77)	1.11 (0.51-2.41)

[δ] *Adjusted for age, sex, race, social deprivation, primary renal diagnosis, vascular co-morbidity, and mode of presentation.*

*$p < 0.05$

**$p < 0.01$

***$p < 0.005$

****$p < 0.001$

Having vascular disease already is the biggest predictor of a major vascular event once dialysis is started. Late referral was associated with higher odds of a vascular event, until adjustment was made for social deprivation. However, the group of patients known to nephrology services but starting dialysis in an unplanned manner, also have a higher risk of having a major vascular event.

Further unadjusted and adjusted Cox regression analysis were done studying the impact of mode of dialysis, serum albumin, serum phosphate, serum calcium, calcium phosphate product, haemoglobin, diastolic blood pressure, systolic blood pressure and cholesterol were performed. None of these factors were associated with major vascular events once dialysis was started (data not shown). This suggests it is dialysis, itself, which results in precipitating vascular events and prevention of vascular disease should occur much earlier.

AIM 1: *To determine whether implementation of current national standards in relation to their achievement or non-achievement, improves outcomes in ESRD patients, receiving dialysis.*

Patients who achieve functioning, permanent access, i.e. an arterio-venous fistula or graft, for haemodialysis (part of the access standard) have improved survival rates. Patients who fail to achieve this are older, female and more socially deprived. Late presentation to renal services is also predictive of failure to achieve this standard. Low serum albumin (an independent predictor of mortality itself) is associated with continuing dialysis with a line. It is not clear whether a low albumin is a result of dialysing with a line, as there are higher sepsis rates and poorer efficiency of dialysis (which is associated malnutrition); or whether a low albumin reflects patients who are already unwell and therefore will not be suitable to undergo access surgery. Given that dialysis with a line is linked to hospitalisation with sepsis, and hospitalisation with sepsis is in turn related to increased mortality, **improving rates of achievement of the access standard, by creating more AV fistulas will almost certainly improve mortality in ESRD patients.**

Failure to achieve the standard for serum phosphate is associated with increased mortality and hospitalisation. There is some evidence that high phosphate levels are related to vascular calcification, and therefore, cardiovascular morbidity and mortality. There is a significant shortfall in achievement of this standard at 1 year (51% of cohort). In addition, it is younger, non-diabetic patients who are more likely to fail to achieve the standard and therefore, have poorer outcomes. There was no association between vascular events and phosphate level in our study, so it remains open to further research to show that intervening to treat phosphate levels directly improves outcomes. **However, there is sufficient data to justify the use of the Renal Association standard for phosphate control as a measure for good treatment on dialysis.**

Interpretation of the impact of the dialysis adequacy standard is more difficult owing to the large proportion of unavailable data, 50% at 1 year. Male patients are more likely not to achieve the standard for adequacy, and they make up two-thirds of the ESRD population. Adequacy is less likely to be measured in patients from ethnic minorities, patients referred late to renal services and patients with diabetic nephropathy. Peritoneal dialysis adequacy is

less likely to be measured than haemodialysis adequacy, but it is peritoneal dialysis that the majority of our cohort are using. In addition, non-measurement of dialysis adequacy, is associated with increased mortality and hospitalisation and reduced odds of receiving a transplant. This suggests it is the more unwell people who do not have adequacy measured. Dialysis adequacy is usually not measured as an inpatient, because of the more unpredictable nature of dialysis performed on inpatients. **This would suggest that other measures for dialysis "adequacy", of which the urea clearance is but one, are used.**

Patients failing to achieve 5, or all 6, of the Renal Association standards for access, haemoglobin, calcium, phosphate, blood pressure and dialysis adequacy, at any time during diaysis treatment, have a poor outcome in terms of mortality. **As these parameters are routinely measured in renal units, further research could be done to see whether these patients could be identified early and treatment be started to improve their outcomes.**

These standards could form the basis of a new definition of dialysis adequacy (not just urea clearance alone), but further research needs to be done, as to achieve this using dialysis would require a significant change in current dialysis practice (e.g. earlier therapy change from PD to HD, daily dialysis, haemodiafiltration, long hours dialysis, more haemodialysis units or home haemodialysis, more staff etc.), as current practice has a significant shortfall in achievement of these standards.

AIM 2: *To assess the impact on outcomes in ESRD patients, receiving dialysis, of non-treatment factors (for example, ethnicity and socio-economic factors) at the start of dialysis treatment.*

Indo-Asian and Black ethnic minority groups are over-represented on RRT. Indo-Asians form the largest minority group, and they are younger than the White ESRD population. There is a strong possibility for rapidly increasing demand for RRT as the general Indo-Asian population in the Northwest grows in size and age.

There is a strong association between belonging to Indo-Asian and having a Townsend score indicating high level of social deprivation. This scoring system is not validated in Asian patients. **Patients with higher levels of social deprivation are at greater risk of having diabetes and being referred late to renal services. This suggests that**

targeting screening programs for the early detection of renal disease to socially deprived areas, including people with diabetes and from ethnic minorities, are likely to produce the biggest benefits in managing chronic kidney disease.

AIM 3: *To assess the impact of mode of referral to nephrology services and dialysis modality, including haemodialysis access, on outcomes in patients with ESRD*

A poorer start to dialysis, with associated poor outcomes, occurred in 2 groups in our study. The first were patients referred late to renal services and the second, patients known to renal services, but having an unplanned start to dialysis.

Patients who were referred within 1 month of requiring dialysis were more likely to be male and socially deprived and have a multisystem disorder causing ESRD or unknown aetiology. They started dialysis with low GFR, serum albumin, serum calcium, haemoglobin, high serum phosphate and started haemodialysis with a line. They have also not received any specialised treatment for renal anaemia (EPO). They have a higher risk of hospitalisation, especially related to sepsis, and higher risk of mortality once on dialysis. This increased risk of mortality is probably related to episodes of sepsis (hospitalisation with sepsis increases subsequent mortality), and possibly poor dialysis. As patients who are referred late have less likehood of achieving the Renal Association standard for access, and dialysing with a line is the strongest predictor of admission with non-CAPD peritonitis, they continue to have poorer outcomes on dialysis. In addition they were less likely to receive a renal transplant during the course of the study. **Improving identification and referral of patients with chronic renal failure, especially targeting susceptible populations, is likely to improve outcomes. In addition, improving the speed at which permanent haemodialysis access is fashioned is likely to improve outcomes.**

Patients who had an unplanned start to dialysis, despite being referred to renal services, are older, more socially deprived and more likely to be single or divorced. They are also more likely to be start dialysis at MRI or Withington. They started dialysis with low GFR, serum albumin, serum calcium, haemoglobin, high serum phosphate and are more likely to start haemodialysis with a line. They did not have increased hospitalisation rates, and no independent risk for sepsis beyond that of starting haemodialysis with a line. They did have an increased risk of having a major vascular event after the initiation of dialysis, despite

having no increased risk of vascular co-morbidity. They were less likely to receive a renal transplant, probably as a result of these vascular events. This group warrants further research. They may have been delayed in starting dialysis because of general ill-health or poor functional state, therefore be felt to be poor candidates for dialysis by physicians; or this group may themselves be reluctant to start dialysis planning until they are unwell and may report few symptoms or they may just have been missed. **There is scope to try to identify these patients and encourage early dialysis planning to improve their outcomes.**

Peritoneal dialysis is utilised to a much larger extent in ESRD patients in the Northwest. But, compared to haemodialysis with a fistula, patients on PD have much higher rates of hospital admissions with sepsis. They are also less likely to have their dialysis adequacy measured. It is perhaps for these 2 reasons, patients on PD have higher mortality than patients on HD with a fistula and patients who change from PD to HD have a lower mortality risk than patients who stay on PD. **Allowing more patients to start haemodialysis with a fistula is likely to improve outcomes, especially admission with sepsis and mortality.**

Starting haemodialysis with a line, associated in particular with late referral, results in higher sepsis rates and higher risk of mortality. **Improving provision and success rates of vascular access is likely to improve patient survival.**

AIM 4: *To report the strongest predictors of outcomes in terms of mortality, transplantation and hospitalisation in patients with ESRD, receiving dialysis.*

Mortality

Age is one of the most significant predictors of mortality. Co-morbid illnesses, in particular vascular disease, myeloma and to a slightly less extent diabetes, have also significant implications for survival on dialysis.

This study shows that albumin level is the strongest biochemical predictor of mortality on dialysis. There are many causes of a low serum albumin. It is an acute phase reactant

protein and is lowered by any systemic inflammation in the body, which may be the cause for the strong association with mortality. Indirect evidence for this is the finding that a high serum ferritin (also an acute phase reactant protein which rises in inflammation) is predictive of mortality. Total iron binding capacity also falls with inflammation, and indeed in our analysis low levels are associated with mortality. Of the other haematological factors, serum iron (not an acute phase reactant), has a modest effect on mortality but at low levels indicating iron deficiency. Low transferrin saturation, probably the most reliable indicator of iron deficiency, was associated with mortality in unadjusted analysis, but was not an independent predictor of mortality. It should be noted that only 30% of our cohort had this measured at baseline. It is not possible to conclude from this study whether correcting iron deficiency will improve mortality, but it suggests that it is a marker of poor outcome and maybe helpful in either ensuring timely initiation of dialysis or predicting survival on dialysis.

Increased inflammation increases the catabolism of the body, which can result in malnutrition. A low body weight was associated with mortality in our study. The association of low blood pressure has been shown in other studies (full discussion chapter 1.3.1) and it postulated to be related to severity of cardiac dysfunction. Low blood pressures are also consistent with patients with chronic or acute systemic inflammation and low serum albumin. In our study low blood pressure (diastolic or systolic) was not related to vascular events after initiation of dialysis.

High serum phosphate levels were found to be independently associated with increased mortality. Using quintiles, a level of 2.18 mmol/l and greater was found to be associated with higher mortality rates. This level is remarkably similar to the level of 2.1 mmol/l Block found in a similar study to be associated with higher mortality in haemodialysis patients *(Block et al. 1998)*. High serum phosphate, along with calcium, are thought to cause coronary artery calcification and by doing so increase cardiovascular mortality in dialysis patients. However, in our study we did not find an association beween serum phosphate and vascular events after the initiation of dialysis.

Starting haemodialysis with a dialysis line has a significant impact on mortality.

Our study suggests, older age, multisystem disorders causing ESRD, co-morbidity, low serum albumin and high serum phosphate are reliable indicators of mortality after initiation of dialysis, and can be used to predict poor outcome. Improving vascular access for haemodialysis and early referral of patients with chronic kidney disease to renal services and subsequent good dialysis planning, will improve outcomes.

Transplantation

Renal transplantation is less likely to be done in older patients and those with vascular co-morbidity. Patients who are married are more likely to receive a renal transplant. Mode of presentation also impacts on transplantation rates as discussed above. Early referral to nephrology services is likely to improve transplantation rates, but in addition nephrologists need to consider whether the bias against referring older patients with co-morbidity needs to be addressed. **The ESRD population is getting older and has more co-morbidity, and it is possible that increasing transplantation in this group will lead to better outcomes, as well as be cost effective to the NHS. Further work needs to be done to suggest benefit versus harm of renal transplantation in this group.**

Hospital Admissions with Sepsis

ESRD who are admitted to hospital with sepsis have a higher subsequent risk of mortality. Dialysis, haemodialysis with a line and peritoneal dialysis, are the biggest causes of sepsis. Late referral is an independent predictor of sepsis admissions and diabetes. So is belonging to the Indo-Asian ethnic group, which may be related to increased exposure to infectious agents, either from visiting the Indian Subcontinent, or having more family members living together, so increasing transmission of infections. **Improving haemodialysis access, improving early referral of patients with chronic kidney disease and using less peritoneal dialysis will reduce hospital admissions with sepsis.**

The biggest predictor of major vascular events is the presence of vascular disease prior to starting dialysis. Patients in the unplanned dialysis group are also at increased risk of vascular events, this may be because they have clinically silent pre-existing vascular disease, but the impact of delayed initiation of dialysis is unknown. There were no biochemical or blood pressure measures which were associated with vascular events post dialysis. **This suggests that there may be other factors which predict vascular events on dialysis. One possibility is that patients already have significant, and sometimes clinically silent, vascular disease at initiation of dialysis and it is something associated with dialysis itself (haemodialysis and peritoneal dialysis) which precipitates further events. To improve outcomes at this stage, treatment for vascular risk factors needs to start much earlier than initiation of dialysis.**

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Appendix 1: ERA-EDTA Primary Renal Diagnosis

Renal Diagnosis	Code
Group 1: Glomerulonephritis	
Glomerulonephritis	10
Focal Segmental glomerulosclerosis with nephrotic syndrome in children	11
IgA nephropathy	12
Membranoproliferative GN; type II	13
Membranous nephropathy	14
Membranoproliferative GN	15
Crescentic glomerulonephritis	16
Focal segmental glomerulosclerosis	17
Glomerulonephritis; histologically examined, not given above	19
Group 2: Interstitial nephritis	
Pyelonephritis cause not specified	20
Pyelonephritis associated with neurogenic bladder	21
Pyelonephritis due to congenital obstructive uropathy with/without vesico-ureteric reflux	22
Pyelonephritis due to acquired obstructive uropathy	23
Pyelonephritis due to vesico-ureteric reflux without obstruction	24
Pyelonephritis due to urolithiasis	25
Pyelonephritis due to other cause	29
Interstitial nephritis cause unspecified	30
Interstitial nephropathy due to analgesic drugs	31
Interstitial nephropathy due to cis-platinum	32
Interstitial nephropathy due to cyclosporin A	33
Lead induced interstitial nephropathy	34
Drug induced interstitial nephropathy	39
Cystic kidney disease	40
Polycystic kidneys; adult type	41
Polycystic kidneys; infantile	42
Medullary cystic disease; including nephronophthisis	43
Cystic kidney disease	49
Hereditary / Familial nephropathy - type unspecified	50
Alport's Syndrome	51
Cystinosis	52
Primary oxalosis	53
Fabry's disease	54
Hereditary nephropathy	59
Renal hypoplasia [congenital] - type unspecified	60
Oligomeganephronic hypoplasia	61
Congenital renal dysplasia with/without urinary tract malformation	63

Renal Diagnosis	Code
Syndrome of agenesis of abdominal muscles	66
Group 3: Multisystem Disorders	
Renal vascular disease	70
Renal vascular disease due to malignant hypertension	71
Renal vascular disease due to hypertension	72
Renal vascular disease due to polyarteritis	73
Wegener's Granulomatosis	74
Ischaemic renal disease / cholesterol embolisation	75
Glomerulonephritis related to liver cirrhosis	76
Cryoglobulinaemic Glomerulonephritis	78
Renal vascular disease - due to other cause	79
Myelomatosis / light chain deposit disease	82
Amyloid	83
Lupus erythematosus	84
Henoch-Schonlein purpura	85
Goodpasture's Syndrome	86
Systemic sclerosis [scleroderma]	87
Haemolytic uraemic Syndrome	88
Multi-system disease - other	89
Tubular necrosis [irreversible] or cortical necrosis	90
Tuberculosis	91
Gout nephropathy	92
Nephrocalcinosis and hypercalcaemic nephropathy	93
Balkan nephropathy	94
Kidney tumour	95
Traumatic or surgical loss of kidney	96
Group 4: Diabetic Nephropathy	
Diabetic Nephropathy (type 1)	80
Diabetic Nephropathy (type 2)	80
Diabetic Nephropathy (type unspecified)	80
Group 5: Unknown/Other	
Other identified renal disorders	99
Chronic renal failure; aetiology uncertain/unknown/unavailable	0